Optimierung der Adhärenz bei Personen mit chronischen Erkrankungen

Prädiktoren, Erfassung, Intervention

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1 Zusammenfassung und Abstract

1.1 Zusammenfassung

Die Non-Adhärenz bei Personen mit chronischen Erkrankungen stellt eine große Herausforderung für das Gesundheitssystem dar. Zwischen 30% und 50% der Patienten[1] nehmen ihre Medikamente nicht wie verordnet ein (Cutler & Everett, 2010; Vermeire, Hearnshaw, van Royen, & Denekens, 2001). Die Gründe für Non-Adhärenz sind individuell und vielseitig (Brawley & Culos-Reed, 2000; Osterberg & Blaschke, 2005; Rief & Nestoriuc, 2015; Vermeire et al., 2001). In der vorliegenden publikationsbasierten Dissertation wurden psychologische Aspekte für Non-Adhärenz, deren Erfassung sowie Prädiktoren zur Erklärung kurzfristiger Schwankungen der Adhärenz näher betrachtet. Zudem wurde eine mögliche Intervention zur Verbesserung des Adhärenzverhaltens bei Personen mit Diabetes mellitus Typ 2 konzeptualisiert.

Bisherige Adhärenzprogramme haben oftmals unbefriedigende Ergebnisse erbracht, nicht zuletzt, da psychologische Risiken für Non-Adhärenz zu wenig berücksichtigt wurden. Aufgrund dessen wurde in der ersten Studie ein narratives Review verfasst, um einen Überblick über psychologische Adhärenz-Risikofaktoren zu geben. Es zeigte sich, dass die Qualität der Arzt-Patienten-Interaktion einen signifikanten Einfluss auf die medikamentöse Adhärenz hat. Weitere Risikofaktoren wie das bisherige Adhärenzverhalten, eine geringe Akzeptanz der eigenen Erkrankung gegenüber, Überzeugungen über die Erkrankung und das Medikament sowie die Angst vor potenziellen Nebenwirkungen eines Medikamentes wurden in bisherigen Adhärenzprogrammen zu wenig berücksichtigt. Zudem sollten die Interventionen an die kognitiven Einschränkungen sowie Komorbiditäten wie z. B. depressive Symptome, adaptiert werden.

In der zweiten Studie wurde ein Screener entwickelt, der unter anderem diese psychologischen Risikofaktoren erfasst. Im Rahmen einer Online-Studie wurde der „Adhärenz Risikoprofil Screener“ (AdRisk) validiert. In die Studie wurden 677

[1] Aus Gründen der Lesbarkeit wird im Folgenden ausschließlich die männliche Form verwendet.

deutschsprachige Personen eingeschlossen, die eine chronische Erkrankung (Diabetes mellitus Typ 2, Bluthochdruck, Epilepsie, chronisch obstruktive Lungenerkrankung, rheumatoide Arthritis oder Morbus Crohn) hatten. Der AdRisk zeigt gute psychometrische Charakteristika. Als ein ökonomisches Screening-Instrument kann das Instrument für unterschiedliche chronische körperliche Erkrankungen im klinischen Alltag eingesetzt werden. Durch die breite Erfassung von unterschiedlichen Barrieren kann der individuelle Unterstützungsbedarf für jeden Patienten abgeleitet werden.

Das Ziel der dritten Studie war es, psychologische Prädiktoren zu identifizieren, die die inkrementelle Varianz in einer kurzfristigen (vierwöchigen) Fluktuation der aktuellen gegenüber der vorherigen Adhärenz erklären können. Mittels Pfadanalysen konnte eine positive Assoziation von Alter, der Qualität der Arzt-Patienten-Interaktion, Stress und die Selbstwirksamkeit in Bezug auf die Medikamenteneinnahme und Adhärenz gezeigt werden. Für die Zufriedenheit mit Wissen über die Medikation und die Ausprägung von Angst konnte ein negativer Zusammenhang gezeigt werden. Diese psychologischen Risikofaktoren konnten, intra-individuelle Schwankungen für eine Non-Adhärenz nach 4 Wochen vorhersagen, die über die erklärte Varianz von der vorherigen Medikamenteneinhaltung hinausgehen.

Im Rahmen der Promotion wurde in einer vierten Studie das Studienprotokoll verfasst, indem ein psychologisches Online-Programm für Personen mit Diabetes evaluiert werden soll. In der Studie soll untersucht werden, inwieweit das diabetesspezifische Onlineprogramm, wenn es zusätzlich zu Care as usual (CAU) angeboten wird, zu einer Verbesserung des Adhärenzverhaltens bei Personen mit Diabetes mellitus Typ 2 führt. Zudem soll geklärt werden, ob die Erwartungen an die Behandlung und die Erkrankung einen mediierenden Effekt haben.

Die Ergebnisse der Dissertation zeigen, dass zur Verbesserung der Adhärenz bei Patienten mit chronischen Erkrankungen die Berücksichtigung psychologischer Aspekte von großer Bedeutung ist. Das Erkennen sowie die systematische Erfassung von psychologischen Risikofaktoren und intra-individuellen Schwankungen sind dafür essentiell. Zudem haben Online-Interventionen mit dem Fokus auf Erwartungen, das Potenzial das Adhärenzverhalten von Patienten zu verbessern.

1.2 Abstract

Non-adherence in persons with chronic diseases is a major challenge for the health care system. Between 30 and 50% of patients do not take their medication as prescribed (Cutler & Everett, 2010; Vermeire et al., 2001). The reasons for non-adherence are individual and multifaceted (Brawley & Culos-Reed, 2000; Osterberg & Blaschke, 2005; Rief & Nestoriuc, 2015; Vermeire et al., 2001). This publication-based dissertation examined, psychological aspects for non-adherence, its assessment, as well as predictors for short-term fluctuations of adherence and a potential intervention to enhance adherence in persons with diabetes mellitus type 2.

Previous adherence programs have often yielded unsatisfactory results, because psychological risks for nonadherence have not been sufficiently considered. In the first study a narrative review was conducted to provide an overview of psychological adherence risk factors. Results showed that the quality of the doctor-patient-interaction has a significant influence on medication adherence. Other risk factors such as previous adherence behavior, a low acceptance of one's own disease, beliefs about the disease and medication as well as the fear of potential side effects were not sufficiently considered in previous adherence programs. In addition, interventions should be adapted to the cognitive impairments and comorbidities, such as depressive symptoms of the patients.

In the second study, a screener was developed which, included these psychological risk factors. In an online study, the "Adherence Risk Profile Screener" (AdRisk) was validated. 677 German-speaking individuals suffering from chronic disease (diabetes mellitus type 2, high blood pressure, epilepsy, chronic obstructive pulmonary disease, rheumatoid arthritis or Crohn's disease) took part of the study. The AdRisk shows good psychometric characteristics. As an economic screening, the instrument can be used for various chronic physical diseases in clinical settings. The broad assessment of different barriers makes it possible to determine the individual needs of each patient.

The aim of the third study was to identify psychological predictors that can explain the incremental variance in a short-term (four-week) fluctuation of current versus previous adherence. Path analyses revealed a positive association of age, quality of doctor-patient

interaction, stress and self-efficacy in terms of drug intake and adherence. We found a negative correlation for the satisfaction with knowledge about medication and the degree of anxiety. Several psychological risk factors predicted intra-individual variations for non-adherence after 4 weeks beyond the explained variance from previous drug adherence.

The fourth study is a protocol of evaluating a psychological online intervention for patients with diabetes. The study will investigate the improvement in adherence behavior of persons with diabetic type 2 if the diabetes-specific online program is offered in addition to Care as usual (CAU). In particular, it should be clarified whether the expectations of the treatment and the disease have a mediating effect.

The findings of the dissertation show that the consideration of psychological aspects is of high relevance for the improvement of adherence in patients with chronic diseases. The identification and systematic assessment of psychological risk factors and predictors of intra-individual fluctuations are essential. In addition, online interventions with a focus on expectations could have the potential to improve adherence behavior.

2 Hintergrund

2.1 Definition Adhärenz

Adhärenz und Compliance sind Begriffe, die häufig verwendet werden, um die Umsetzung medizinischer Empfehlungen zu beschreiben (Garcia-Perez, Alvarez, Dilla, Gil-Guillen, & Orozco-Beltran, 2013). Compliance beschreibt das Ausmaß, in dem sich Patienten an die vom Arzt vorgegebenen Instruktionen und Verschreibungen halten. Die Begriffe Adhärenz und Compliance werden oft synonym verwendet und in der Literatur nicht ausreichend differenziert (Barbosa, Balp, Kulich, Germain, & Rofail, 2012), obwohl sie sich in wichtigen Aspekten unterscheiden.

Im Jahre 2003 veröffentlichte die Weltgesundheitsorganisation (engl. World Health Organization; WHO) die folgende Definition für Adhärenz:

"The extent to which a person's behavior – taking a medication, following a diet and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (Sabaté, 2003).

Diese Definition wird in der vorliegenden Arbeit ausschließlich verwendet und soll anhand der folgenden Punkte kurz erläutert werden. Erstens betrifft diese Adhärenzdefinition eine Mehrzahl von Verhaltensweisen. Jedoch lag der Fokus wissenschaftlicher Studien bisher oft nur auf der Einnahme von Medikamenten. Das Konzept der Adhärenz wurde im Unterschied zu Compliance jedoch um weitere relevante Faktoren, die einen Einfluss haben, erweitert. So zeigt sich, dass ein gesunder Lebensstil einschließlich einer gesunden Ernährung und einer Erhöhung der körperlichen Aktivität, eine wichtige Rolle spielen und mit einer niedrigeren Morbidität und Mortalität bei Personen mit chronischen Erkrankungen assoziiert sind (Haveman-Nies, 2003; Pronk et al., 2004). Der zweite wichtige Aspekt der Definition ist, dass ein Patient den Empfehlungen des Arztes oder eines anderen Mitarbeiters des Gesundheitssystems ausdrücklich zustimmt und den Behandlungsplan beeinflussen kann (Schäfer, 2017). Adhärenz beschreibt also, ob und in welchem Ausmaß die Behandlungsempfehlungen umgesetzt werden, die Behandler und Patient in einer partizipativen Entscheidungsfindung festgelegt haben (Schäfer, 2017).

Individualität und die Lebensumstände des Patienten sollten berücksichtigt werden (Sabaté, 2003). Dieser partizipative Ansatz beinhaltet, dass Patienten über verschiedene Behandlungsmöglichkeiten informiert werden und aktiv die praktikabelste und vielversprechendste Option für sich auswählen können (Schäfer, 2017). Dies stellt auch den Hauptunterschied zwischen den Konzepten Adhärenz und Compliance dar.

Die Verbesserung der Adhärenz stellt eine der größten Herausforderungen für das Gesundheitssystem dar. 30% - 50% der Personen, bei denen eine chronische Erkrankung diagnostiziert wurde, nehmen ihre Medikamente nicht wie verordnet ein (Vermeire et al., 2001). Dies gilt für verschiedene medizinische Präparate wie Neuroleptika, Diabetesmedikation o.a. und unterschiedliche Patientengruppen (Dimatteo, 2004a; Sabaté, 2003). Die in der Literatur berichteten Adhärenzraten sind üblicherweise niedriger bei Personen mit chronischen als akuten Erkrankungen (Osterberg & Blaschke, 2005). Es zeigt sich Evidenz dafür, dass Adhärenzraten nach der Diagnose einer chronischen Erkrankung innerhalb der ersten sechs Monate dramatisch sinken (Serna, Cruz, Real, Gascó, & Galván, 2010). Im Kontext von chronischen Erkrankungen lässt sich Adhärenz in drei Phasen einteilen. Diese umfassen sowohl die Initiierung der Behandlung sowie die Implementierung des individuellen Behandlungskonzeptes als auch die Persistenz/Kontinuität der Behandlung (Vrijens et al., 2016). In einer repräsentativen deutschen Studie konnte jedoch gezeigt werden, dass Non-Adhärenz ein weitverbreitetes, menschliches und krankheitsunspezifisches Verhalten ist (Glombiewski, Nestoriuc, Rief, Glaesmer, & Braehler, 2012).

Die Folgen einer geringen Adhärenz bei chronischen Erkrankungen sind immens, da es zu einer geringeren Wirksamkeit der Behandlung kommt und daraus eine höhere Sterblichkeit resultiert. Zudem erhöhen sich die Kosten für das Gesundheitssystem (Sabaté, 2003). In einer Metaanalyse basierend auf 63 Studien konnte über unterschiedliche Erkrankungen hinweg gezeigt werden, dass durch adhärentes Verhalten das Risiko von negativen Folgen, wie beispielsweise Infektionen oder Herzinfarkte, um 26 % gesenkt werden konnte (Dimatteo, Giordani, Lepper, & Croghan, 2002). Es gibt Hinweise darauf, dass psychologische Interventionen das Potenzial haben, die Adhärenz von Personen mit chronischen Erkrankungen zu verbessern (Conn, Ruppar, Chase, Enriquez, & Cooper, 2015; Dimatteo, 2004b; Peterson, Takiya, & Finley, 2003; Zolnierek, & Dimatteo, 2009). Daher ist

es essentiell, auch psychologische Aspekte für Non-Adhärenz zu betrachten und in die Versorgung zu integrieren.

2.2 Theorien und Modelle des Gesundheitsverhaltens

Das Health Belief Model (HBM) (Rosenstock, 1974) und das Common Sense-Selbstregulationsmodell (CSM) (Leventhal, Phillips, & Burns, 2016; Leventhal & Ian, 2012) werden häufig zur Erklärung von Gesundheitsverhalten verwendet. Rob Horne hat das CSM zur Vorhersage von Adhärenz adaptiert (Horne, 2003; Horne, Weinman, & Hankins, 1999).

Als eines der ersten Modelle wurde das HBM zur Erklärung von Gesundheits- und Risikoverhalten entwickelt. Das Modell postuliert, dass Gesundheitsverhalten durch die subjektiv erlebte gesundheitliche Bedrohung durch eine Erkrankung sowie den Erwartungen an Kosten vs. Nutzen der Behandlung bedingt wird (Lippke & Renneberg, 2006; Rosenstock, 1974). Die wahrgenommene Bedrohung durch die Erkrankung beinhaltet Aspekte der wahrgenommenen Verwundbarkeit (z. B. „ich habe ein erhöhtes Risiko eine chronische Erkrankung zu bekommen“) und des Schweregrads (z. B. „so eine chronische Erkrankung kann tödlich sein“). Nach dieser Einschätzung folgt eine Bilanzierung aus den Kosten (z. B. „die Medikamente haben starke Nebenwirkungen“) und den Nutzen (z. B. „mit einer regelmäßigen medikamentösen Behandlung verringert sich die Wahrscheinlichkeit von Folgeerkrankungen“) der Behandlung. Zudem integriert das HBM den Einfluss von demographischen und psychologischen Charakteristika sowie die individuelle Gesundheitsmotivation und Handlungsreize (Lippke & Renneberg, 2006). In Metaanalysen konnten geringe Zusammenhänge zwischen den einzelnen Komponenten und der Intention für funktionales Gesundheitsverhalten gezeigt werden, wobei die Kosten oder Barrieren die besten Prädiktoren waren (Carpenter, 2010; Harrison, Mullen, & Green, 1992).

Am HBM wurde jedoch auch Kritik geübt, da einige Modellkomponenten kaum untersucht wurden und die korrelativen Zusammenhänge sehr gering ausfielen. Dies spricht dafür, dass möglicherweise andere, besser geeignete Prädiktoren von Gesundheitsverhalten nicht im Modell berücksichtigt werden (Lippke & Renneberg, 2006).

Das CMS ist eines der bekanntesten Modelle zur Vorhersage von Gesundheitsverhalten. Es basiert auf der Annahme, dass bei einer potenziellen oder tatsächlichen

Gesundheitsbedrohung ein Selbstregulationsprozess aktiviert wird. Im Rahmen des CSM wird angenommen, dass Personen subjektive Vorstellungen über die Erkrankung oder das Ausmaß der Bedrohung haben. Diese werden in dem Modell als *kognitive Repräsentationen* bezeichnet. Auf empirischer Basis konnten die folgenden fünf Repräsentationen nachgewiesen werden: die wahrgenommenen Symptome der Erkrankung (Identity), der zeitliche Verlauf (Timeline), die Konsequenzen (Consequences), Ursachen (Cause) sowie die persönliche und Behandlungskontrolle (Personal-, & Treatmentcontrol) der Erkrankung (Glattacker & Heyduck, 2016). Diese subjektiven Vorstellungen steuern die Auswahl, Ausführung und Aufrechterhaltung von Bewältigungsverhalten (Coping) wie z. B. die Einnahme von Medikamenten. Im Anschluss wird das Bewältigungsverhalten hinsichtlich des Ergebnisses bewertet und gegebenenfalls erneut durchlaufen (selbstregulativer Prozess). Parallel dazu postuliert das Modell, dass auch immer eine emotionale Reaktion wie z. B. Angst, Ärger oder Traurigkeit erfolgt, die als *emotionale Repräsentation* bezeichnet wird.

Rob Horn (2003) adaptierte das CSM für die Vorhersage von Adhärenz (Abbildung 1) und erweiterte es um die *kognitive* und *emotionale Behandlungsrepräsentation*.

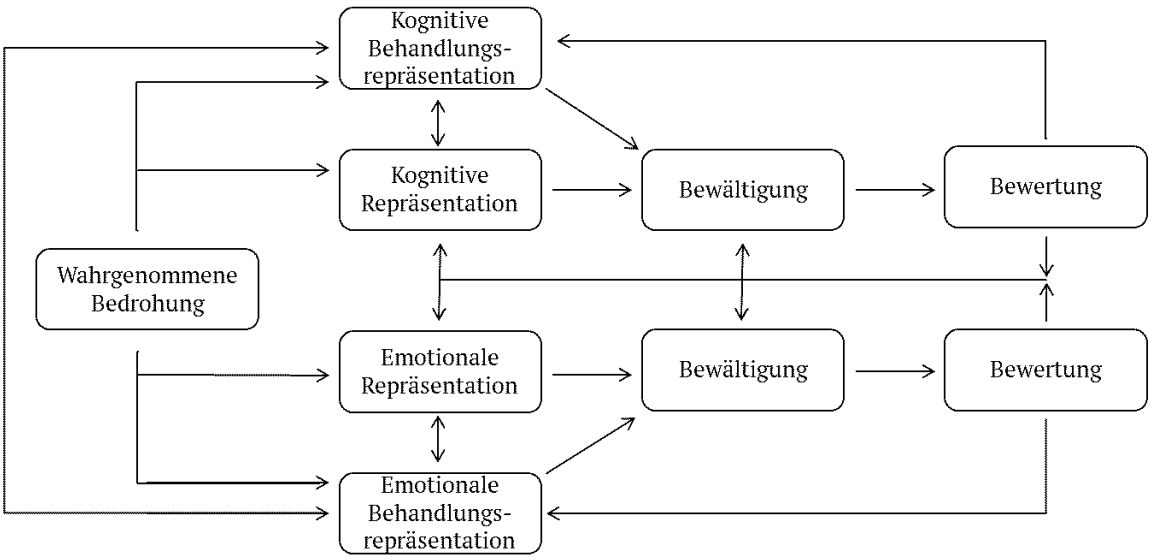

Abbildung 1. Die Adaptation des Common Sense-Selbstregulationsmodell (CSM) nach Horne (2003)

Im Sinn einer Kosten-Nutzen-Analyse wägen Patienten zwischen der Notwendigkeit (Necessity) und den Bedenken (Concerns) bezüglich der Behandlung ab (Horne, 2003). Das Ergebnis dieser Abwägung entscheidet, ob ein Patient sich adhärent oder non-adhärent verhält. Laut Modell erhöht sich die Wahrscheinlichkeit adhärenten Verhaltens, wenn die subjektiv wahrgenommene Notwenigkeit höher eingeschätzt wird als die Bedenken bezüglich der Behandlung (Horne et al., 2013). Die Gültigkeit dieses Modells konnte bereits in einigen Studien nachgewiesen werden (Foot, La Caze, Gujral, & Cottrell, 2016; Horne et al., 2013; Wilhelm, Rief, & Doering, 2018).

2.3 Ursachen für Non-Adhärenz

In der Literatur wird empfohlen, wenigstens zwei Arten von Non-Adhärenz zu unterscheiden, nämlich die unabsichtliche und absichtliche Non-Adhärenz (Rief & Nestoriuc, 2015). Bei der unabsichtlichen Non-Adhärenz ist der Patient grundsätzlich bereit, sich an den zuvor festgelegten Behandlungsplan zu halten, kann dies aber aufgrund fehlender Ressourcen nicht. Zu unabsichtlicher Non-Adhärenz kommt es bspw. durch das Vergessen der Einnahme, Informations- oder Kompetenzdefizite und kognitive Defizite (Rief & Nestoriuc, 2015). Unter absichtlicher Non-Adhärenz versteht man im Gegensatz dazu das bewusste Missachten der Behandlungsempfehlung (Horne et al., 2013). Diese Art der Non-Adhärenz macht den deutlich größeren Teil non-adhärenten Verhaltens aus (Rief & Nestoriuc, 2015). Die vielfältigen individuellen Gründe für absichtliche Non-Adhärenz zu verstehen ist essentiell für die Entwicklung und Verbesserung möglicher Interventionen.

Nach Einteilung der WHO haben die folgenden fünf Faktoren einen Einfluss auf die Adhärenz (Sabaté, 2003): sozioökonomische Faktoren, Faktoren bedingt durch das Gesundheitssystem, therapiebezogene Faktoren, krankheitsspezifische Faktoren und patientenbezogene Faktoren.

Sozioökonomische Faktoren. Zu den sozioökonomischen Faktoren, die mit Adhärenz assoziiert sind, gehören Alter, Geschlecht, Bildungsniveau (u. a. Lesekompetenz), Berufstätigkeit, finanzielle Situation (sozioökonomischer Status, Einkommen, materielle Ressourcen), Art der Krankenversicherung, Ethnizität und Kultur (Sprachbarrieren,

Herkunft, Migrationsstatus) sowie die Wohnsituation (fester Wohnsitz, alleinstehend, Partnerschaft) (Allemann, Nieuwlaat, van den Bemt, Hersberger, & Arnet, 2016). In der Metaanalyse von DiMatteo (2004a) konnte ein kleiner Effekt von sozioökonomischen Variablen auf Adhärenz nachgewiesen werden. Dieser wurde jedoch moderiert durch die Charakteristika der Stichproben, der Art der Behandlung und Erkrankung sowie der verwendeten Messinstrumente.

Faktoren bedingt durch das Gesundheitssystem. Bezüglich der Faktoren des Gesundheitssystems sind die Interaktion des Patienten mit dem Arzt oder dem medizinischen Fachpersonal (Robinson, Callister, Berry, & Dearing, 2008; Sabaté, 2003), die Verfügbarkeit von Behandlungen (z. B. Systemkapazität) (Sherman et al., 2009) sowie die Aufklärung der Patienten (z. B. Schulungen) (Ryan et al., 2014) Gegenstand der Adhärenzforschung. Im Vordergrund steht hier oft die Interaktion des Patienten mit dem Arzt und dem medizinischen Fachpersonal (Sabaté, 2003). Rubin, Peyrot & Siminerio (2006) konnten eine positive Korrelation zwischen der Qualität der Behandler-Patienten-Beziehung und der medikamentösen Adhärenz sowie der Veränderung von Lebensweisen bei Personen mit Diabetes nachweisen. Dieser Effekt konnte auch langfristig nachgewiesen werden (Arnold-Wörner, 2005).

Therapiebezogene Faktoren. Therapiebezogenen Faktoren, die häufig mit Non-Adhärenz assoziiert werden, sind eine höhere Komplexität des Medikamentenregimes (Ingersoll & Cohen, 2008), viele Änderungen innerhalb der Behandlung (Schäfer-Keller, Garzoni, Dickenmann, & Geest, 2010), die Dauer der Behandlung (Schäfer-Keller et al., 2010), das bisherige Ansprechen auf die Behandlung (Zeber et al., 2013) und das Auftreten von Nebenwirkungen (Ingersoll, & Cohen, 2008; Sabaté, 2003; Zeber et al., 2013). In einer Studie konnte gezeigt werden, dass Personen, deren medikamentöse Behandlung weniger Nebenwirkungen verursachte, eine signifikant höhere Adhärenzrate aufwiesen (Pollack, Purayidathil, Bolge, & Williams, 2010).

Krankheitsspezifische Faktoren. Zudem konnten die Chronizität der Erkrankung (Zeber et al., 2013), die Schwere der Erkrankung (Schäfer-Keller et al., 2010) sowie der Grad der subjektiven Beeinträchtigung, die Progressionsrate, Komorbiditäten und die Verfügbarkeit

wirksamer Therapien (Sabaté, 2003) als Faktoren assoziiert werden, die bei spezifischen Erkrankungen die Adhärenz vorhersagen.

Patientenbezogene Faktoren. In der Literatur werden kognitive Einschränkungen (Baudrant-Boga, Lehmann, & Allenet, 2012), Komorbiditäten (Zeber et al., 2013), frühere Non-Adhärenz (Rief & Nestoriuc, 2015) sowie die Angst vor Nebenwirkungen, psychosozialer Stress und das Wissen über die Erkrankung (Sabaté, 2003) als patientenbezogene Prädiktoren für Adhärenz berichtet. Weiterhin wird oft auch das Ausmaß an individuell wahrgenommener Selbstwirksamkeit diskutiert (Ashford, Edmunds, & French, 2010). Zudem können Wahrnehmungen und Überzeugungen über die Erkrankung sowie die Behandlung die Adhärenz beeinflussen (Horne, Weinman, & Hankins, 1999). Die Überzeugung über die Notwendigkeit einer Behandlung wurde als einer der wichtigsten Prädiktoren zur Vorhersage von Adhärenz bei unterschiedlichen Erkrankungen in einer Vielzahl von Studien nachgewiesen. Im Gegensatz dazu können Bedenken in Bezug auf Medikamente oder andere Behandlungsoptionen ein entscheidendes Hindernis für die Einhaltung darstellen (Clatworthy et al., 2009; Horne, Cooper, Gellaitry, Date, & Fisher, 2007; Tibaldi et al., 2009). Bedenken hinsichtlich der Behandlung beinhalten vor allem die Angst vor Nebenwirkungen, sind jedoch nicht auf diese beschränkt. Ebenso relevant ist die Angst vor Langzeitfolgen oder Abhängigkeit von Medikamenten (Horne et al., 2013).

Zusammenfassend lässt sich feststellen, dass oft jedoch nicht nur ein Faktor die unzureichende Adhärenz bedingt, sondern es sich um ein multifaktorielles Geschehen handelt. Die WHO weist ausdrücklich darauf hin, dass es sich um einen veränderbaren Prozess handelt, der zeitlichen Schwankungen des Krankheitsverlaufs unterliegt (Sabaté, 2003).

2.4 Erfassung von Non-Adhärenz

Um die Adhärenz von Personen mit chronischen Erkrankungen zu verbessern, ist es zunächst wichtig, die Non-Adhärenz sowie spezifische Faktoren, die einen Einfluss haben können, zu identifizieren (Hahn et al., 2008). Doch auch nach vier Jahrzehnten der Forschung existiert kein „Goldstandard“ zur Erfassung individueller Gründe von Non-

Adhärenz (Lam & Fresco, 2015). Die Erfassung eines individuellen Risikoprofils wäre allerdings der erste notwenige Schritt, um den individuellen Unterstützungsbedarf ableiten zu können und maßgeschneiderte adhärenzsteigernde Interventionen zu entwickeln.

Die Erfassung von Non-Adhärenz ist eine schwierige Aufgabe, da eine Vielzahl von Risikofaktoren und Unterschieden zwischen den Erkrankungsarten existieren (Hahn et al., 2008). Zudem lässt sich Adhärenz in drei Phasen einteilen und umfasst dabei die Initiierung der Behandlung, die Implementierung des individuellen Behandlungskonzeptes sowie die Kontinuität der medikamentösen Behandlung (Vrijens et al., 2016).

Adhärenz zu einer medikamentösen Behandlung kann sowohl über objektive als auch subjektive Verfahren gemessen werden (Lam & Fresco, 2015). Objektive Verfahren sind die Beobachtung der Einnahme (z. B. über elektronische Überwachungssysteme) oder die Überprüfung der Auffüllraten (z. B. Frequenz eingelöster Rezepte) (Lam & Fresco, 2015). Des Weiteren kann die Bestimmung des Medikamentenspiegels im Blut oder im Urin erfolgen (Lam & Fresco, 2015). Diese objektiven Verfahren sind im klinischen Alltag aufgrund des hohen Aufwandes und der Kosten nur eingeschränkt nutzbar (Hahn et al., 2008). Zudem kann die Überwachung die Offenheit und das Vertrauen des Patienten zu seinem behandelnden Arzt gefährden (Hahn et al., 2008).

Daher wird die Adhärenz im klinischen Alltag oft subjektiv über Selbstbeobachtungsfragebögen erfasst (Simpson et al., 2006). Damit können sowohl Behandler oder Arzt als auch die Patienten systematisch befragt werden. Allerdings liegen bei diesem Verfahren in aller Regel Verzerrungen vor, so überschätzen Ärzte und Patienten üblicherweise die Adhärenz (Osterberg & Blaschke, 2005). Dies sollte unbedingt im klinischen Alltag berücksichtigt werden.

Adhärenz kann dichotom (nimmt das Medikament oder nicht) oder auf einem Kontinuum gemessen werden (Lam & Fresco, 2015). Selbstbeobachtungsfragebögen, die bisher zur Erfassung von Adhärenz eingesetzt wurden, messen oft nur, ob und in welchem Ausmaß eine Person adhärent ist, wie beispielsweise die Medication Adherence Report Scale (MARS) (Mahler et al., 2010) oder die Morinsky Medication Adherence Scale (MMAS) (Morisky, Ang, Krousel-Wood, & Ward, 2008). Der Rief Adherence Index (RAI) ist ein Kurz-Screener, der das frühere Adhärenzverhalten erfragt, um so eine Vorhersage auf die aktuelle

Adhärenz machen zu können, ganz nach dem Grundsatz - past behavior predicts future behavior (Glombiewski et al., 2012). Andere Selbstbeobachtungsfragebögen haben sich auf einen spezifischen Bereich der Adhärenz festgelegt wie der Beliefs about Medicine Questionnaire (BMQ) (Horne et al., 1999). Dieser wurde entwickelt, um potenziell ungünstige Einstellungen zur Behandlung zu erfassen. Ein sinnvoller Ansatz für den klinischen Alltag scheint die möglichst breite Erfassung potenzieller Adhärenzbarrieren zu sein (Müller, Kohlmann, & Wilke, 2015). Der Adhernce Barriers Questionnaire (ABQ) beispielsweise erfasst mit 15 Items unterschiedliche Aspekte, die den folgenden drei Barrieren zugeordnet werden können: intentionale (absichtliche) Adhärenz- Barrieren (Einstellungen oder negative Überzeugungen der Behandlung oder Medikation gegenüber), unintentionale (unabsichtliche) Adhärenz-Barrieren (Vergesslichkeit, Depression, mangelndes Wissen) und Barrieren bezüglich des Gesundheitssystems (Zusatzkosten oder Zuzahlungen, fehlende Unterstützung, spezielle Eigenschaften des Medikamentes) (Müller et al., 2015).

Zusammenfassend zeigt sich Evidenz für die Relevanz verschiedener Einflussfaktoren auf die Adhärenz von Patienten (Brawley & Culos-Reed, 2000; Osterberg & Blaschke, 2005; Rief, & Nestoriuc, 2015; Vermeire et al., 2001), zu deren Erfassung auch Instrumente entwickelt wurden. In diesen wurden die Medikamenteneinnahme, verschiedene Barrieren und Erwartungen/ Überzeugungen (oder eine Kombination aus diesen) erfasst (Nguyen, La Caze, & Cottrell, 2014). Allerdings gibt es bislang nur eine begrenzte Möglichkeit, eine Vielzahl von Barrieren bei unterschiedlichen chronischen Erkrankungen zu erfassen. Zudem haben die Fragebögen oft sehr viele Items und können daher nicht zur ökonomischen Erfassung im klinischen Alltag eingesetzt werden.

2.5 Online-Programme zur Förderung von Adhärenz bei Diabetes mellitus Typ 2

Diabetes mellitus ist eine weitverbreitete chronische Stoffwechselerkrankung, die durch eine erhöhte Blutzuckerkonzentration (Hyperglykämie) gekennzeichnet ist (Bundesärztekammer, 2013). Diese Erhöhung kann die Folge einer gestörten

Insulinsekretion und/oder Insulinwirkung sein. Nach Schätzungen der International Diabetes Federation (IDF) aus dem Jahre 2018 haben weltweit 425 Millionen Personen eine Diabeteserkrankung. Derzeit sind in Deutschland etwa 6.7 Millionen Personen betroffen, darunter werden etwa 2 Millionen geschätzt, deren Diabetes mellitus noch nicht erkannt wurde (DiabetesDE, 2018). Circa 95% der Personen, bei denen Diabetes diagnostiziert wurde, haben Diabetes mellitus Typ 2 (DiabetesDE, 2018).

Adhärenz ist ein großes Problem bei Personen mit Diabetes (King, Mainous, Carnemolla, & Everett, 2009). Eine gute Kontrolle des Blutzuckers erfordert einige komplexe Verhaltensweisen. Zu diesen zählen ein gesundes Ernährungsverhalten, eine adäquate körperliche Aktivität, eine regelmäßige Messung des Blutzuckers, die Einhaltung von zuvor festgelegten Arztbesuchen sowie eine regelmäßige medikamentöse Behandlung (IDF, 2018; Schmitt et al., 2013). Adhärenz bezüglich der medikamentösen Behandlung von Diabetes variiert zwischen 36%-93% für die Einnahme von oralen Präparaten sowie der Behandlung mit Insulininjektionen (Cramer, 2004). Die Schwankungen der verfügbaren Adhärenzraten kommen durch unterschiedliche Faktoren zustande. Dies kann an der Zusammensetzung der Stichprobe (z. B. Unterschiede des sozioökonomischen Status) als auch an konzeptuell-methodischen Unterschieden wie der Definition und der Erfassung von Adhärenz (z. B. Festlegung des Cut-off Wertes) liegen (Garcia-Perez et al., 2013; Guillausseau, 2003). Die Adhärenz für die Nutzung von Programmen, die zur Förderung der körperlichen Aktivität eingesetzt werden, liegt zwischen 10% und 80% (Praet & van Loon, 2009). Zusammenfassend zeigt sich jedoch, dass weniger als 50% der Personen mit einem diagnostizierten Diabetes ihre glykämischen Ziele erreichen (Cramer, 2004), obwohl es verschiedene effektive Therapiemöglichkeiten für die entsprechenden Stadien der Erkrankung gibt. Die Folgen von Non-Adhärenz bei Diabetes sind gravierend. So führt Hyperglykämie zu einer Vielzahl von Folgeerkrankungen (akut und chronisch), mehr Krankheitstagen und Krankenhausaufenthalten, einer niedrigeren Lebenserwartung und neben der Belastung für den Betroffenen auch zu immensen Kosten für das Gesundheitssystem (DiabetesDE, 2018; Heidemann, Du, & Scheidt-Nave, 2015).

Die kognitive Verhaltenstherapie (englisch: cognitive behavioral therapy; CBT) hat sich als wirksam erwiesen, um Aspekte des Adhärenzverhaltens bei Personen mit Diabetes zu verbessern (Ismail, Winkley, & Rabe-Hesketh, 2004). Eine Metaanalyse psychologischer

Interventionen in randomisiert kontrollierten Studien (englisch: randomized controlled trials; RCTs) zeigte eine Verbesserung der langfristigen Blutzuckerkontrolle und die Reduktion von Stress (Ismail, Winkley, & Rabe-Hesketh, 2004). Allerdings konnte keine Reduktion des Gewichtes oder des durchschnittlichen Blutzuckerspiegels der letzten 8 bis 10 Wochen (gemessen durch den HbA1c-Wert), nachgewiesen werden (Ismail et al., 2004). Elemente der CBT waren unter anderem das Erlernen von Entspannungstechniken, die Vermittlung von Problemlösestrategien, die Anleitung zur eigenständigen Zielsetzung und Selbstbeobachtungen sowie die Integration von sozialer Unterstützung in die Behandlung. Diese Interventionen wurden meistens im direkten Kontakt (englisch: face-to-face setting) (Garcia-Perez et al., 2013) oder in Gruppen (englisch: group setting) (Ismail et al., 2004; Snoek et al., 2001) dargeboten. Möglicherweise sind diese Settings jedoch nicht für alle Personen mit Diabetes gleichermaßen geeignet. Zudem zeigt sich, dass evidenzbasierte Interventionen, die auf die Bedürfnisse der Betroffenen individuell angepasst sind, stark limitiert sind (Ramadas, Quek, Chan, & Oldenburg, 2011). In unserer globalen Welt, in der die Digitalisierung zunehmend von Bedeutung ist, sind Online-Programme daher eine vielversprechende Erweiterung (Donkin et al., 2011; Morrow et al., 2012).

Online-Programme haben einige Vorteile, die im Folgenden kurz genannt werden sollen. So können sie von einer Vielzahl von Personen gleichzeitig genutzt werden (Donkin et al., 2011), sind bequem von Zuhause abrufbar und können zeitlich flexibel (24-Stunden täglich) genutzt werden (Glasgow, Boles, McKay, Feil, & Barrera, 2003). Des Weiteren gewährleisten sie den Betroffenen Anonymität und bieten die Möglichkeit, komplexe Informationen in Form von Videos und Grafiken leicht verständlich darzustellen (Rowsell et al., 2015). Regelmäßige Updates können das Programm in kurzer Zeit auf den aktuellen Stand bringen und neue wissenschaftliche Erkenntnisse integrieren. Darüber hinaus besteht die Möglichkeit, interaktive Elemente zu implementieren und so die individuellen Bedürfnisse zu berücksichtigen (Vandelanotte, Spathonis, Eakin, & Owen, 2007).

Metaanalysen zeigen die Effektivität von internetbasierten Interventionen mit kognitiv-verhaltenstherapeutischem Schwerpunkt (englisch: internet-based cognitive-behavioural interventions; ICBT) bei unterschiedlichen somatischen Erkrankungen wie Tinnitus (Jasper et al., 2014), Epilepsie oder chronischen Schmerzen (van Beugen et al., 2014). In einem Review von Ramadas und Kollegen (2011) wurden auch Interventionen für

Personen mit Diabetes Typ 2 Wirksamkeit attestiert. Die effektivsten, zum Teil interaktiven Elemente waren Zielsetzung, direktes Feedback, Selbstbeobachtung, personalisiertes Coaching und die Nutzung von Chatrooms, in denen Betroffene die Möglichkeit zum Austausch hatten. Eine weitere Metaanalyse überprüfte die Effektivität von kognitiv-verhaltenstherapeutischen Online-Programmen zur Verbesserung der körperlichen Aktivität bei Personen mit Diabetes (Davies, Spence, Vandelanotte, Caperchione, & Mummery, 2012). In die Analyse wurden 34 Studien eingeschlossen. Es fand sich gemäß den Konventionen von Cohen (1988) ein kleiner Effekt von $d = 0.14$. In einer anderen internetbasierten Studie zur Verbesserung der körperlichen Aktivität konnte nach 12 Wochen eine Effektstärke von $d = 0.27$ und nach 36 Wochen eine Effektstärke von $d = 0.11$ nachgewiesen werden (Jennings, Vandelanotte, Caperchione, & Mummery, 2014).

Insgesamt zeigen sich erste Hinweise, dass sowohl Wissen über die Erkrankung sowie die Aufklärung über die möglichen Folgen von Diabetes, Elemente sind, die zu einer Verbesserung der glykämischen Kontrolle führen können (Pal et al., 2013; Ramadas et al., 2011). Zudem hatte auch die Implementierung von Entspannungstechniken wie Imaginations-, Atem- und körperlichen Übungen (z. B. autogenes Training und progressive Muskelentspannung) einen positiven Effekt.

Allerdings ist auch die Adhärenz der Nutzung von internetbasierten Programmen oft nicht perfekt und kann durch Erinnerungssysteme (z. B. tägliche Textnachrichten oder Telefonanrufe) verbessert werden (Kelders, Kok, Ossebaard, & van Gemert-Pijnen, 2012; Melville, Casey, & Kavanagh, 2010).

Es gibt Belege, dass die Erwartungen bezüglich der Behandlung von Patienten durch psychologische Interventionen beeinflusst werden können (Laferton, Shedden Mora, Auer, Moosdorf, & Rief, 2013). Diese Interventionen zielen auf die kognitive Repräsentation der Erkrankung und deren Behandlung ab, zudem werden emotionale Aspekte berücksichtigt (Heisig et al., 2016). Erste Studien deuten darauf hin, dass Interventionen mit dem Fokus auf Erwartungen bezüglich des Therapieerfolges bei Personen mit Diabetes wirksam sein können, um das Adhärenzverhalten zu verbessern (Keogh et al., 2007; Wu et al., 2007). Snoek und Kollegen (2001) untersuchten eine Intervention, die sich auf die Identifizierung und Veränderung negativer Erwartungen von Personen mit Diabetes mellitus Typ 1

konzentrierte. Die Intervention führte zu einem verbesserten Selbstbehandlungsverhalten im Hinblick auf eine regelmäßige Blutzuckerkontrolle und eine erhöhte Einhaltung des Diät- und Bewegungsverhaltens (Snoek et al., 2001). Es gibt bislang jedoch keine vergleichbaren Studien für Personen mit Diabetes mellitus Typ 2.

Zusammenfassend zeigten sich in bisherigen Metaanalysen nur kleine, kurzfristige Effekte von internetbasierten Selbstbehandlungsprogrammen bei Personen mit Diabetes mellitus Typ 2 (Pal, 2013). In den letzten Jahren wurden zunehmend Online-Programme zur Verbesserung des Adhärenzverhaltens entwickelt (Vandelanotte et al., 2007), allerdings wurden hier oft nur Aspekte der Diabetesbehandlung wie die Ernährungsweise (Armstrong & Powell, 2008), die körperliche Aktivität (Glasgow et al., 2003) oder auch die Veränderung des Langzeitwertes (HbA1c-Wert) (Noh et al., 2010) untersucht. Psychologische Interventionen, die auf eine nachhaltige Verhaltensänderung, verbesserte Medikamentenadhärenz sowie Erwartungsveränderungen abzielen, wurden bisher kaum erforscht (McKay, Glasgow, Feil, Boles, & Barrera, 2002).

3 Darstellung des Dissertationsvorhabens

3.1 Relevanz und Herleitung der Fragestellung

Wie bereits weiter oben erläutert, werden in der Literatur eine Vielzahl von Faktoren beschrieben, die einen Einfluss auf die Adhärenz bei Personen mit chronischen Erkrankungen haben z. B. sozioökonomische Faktoren u. a. (Sabaté, 2003). Allerdings ist der Fortschritt auch nach vier Jahrzehnten der Forschung in Bezug auf die medikamentöse Adhärenz enttäuschend und die Non-Adhärenzraten weiterhin konstant hoch (Allemann et al., 2016). In den unterschiedlichen Dekaden wurden verschiedene Modelle, die das Adhärenzverhalten erklären sollen, wie z. B. Common-Sense Modell of Self Regulation, diskutiert und erweitert (Horne et al., 1999). Zunehmend gab es qualitative Studien, die den Fokus auf die Arzt-Patienten-Interaktion und die Überzeugungen (über Erkrankung oder Behandlung) des Patienten legten (Vermeire et al., 2001). Ansätze mit einer biomedizinischen Betrachtungsweise, operanter Konditionierung, sozialen Lerntheorien, Kommunikationsmodellen und Selbstregulationstheorien wurden entwickelt, jedoch ohne konsistente Erfolge zu erzielen (Nieuwlaat et al., 2014). In der Praxis wurden eine Menge Interventionen implementiert, um die Adhärenz der Patienten zu verbessern, jedoch konnten in Metaanalysen nur kleine Effekte nachgewiesen werden (Conn et al., 2015; Peterson et al., 2003). Möglicherweise haben bisherige Adhärenzprogramme oftmals unbefriedigende Ergebnisse erbracht, da einigen psychologischen Risikofaktoren für Non-Adhärenz zu wenig Aufmerksamkeit geschenkt wurde. Diese könnten dann in zukünftigen Interventionen berücksichtigt und zu einer Erhöhung der Adhärenz beitragen.

Bislang wurden verschiedene Skalen zur Erfassung einzelner oder einer bestimmten Auswahl von Prädiktoren entwickelt, die mit Non-Adhärenz assoziiert sind. Diese Messinstrumente wurden entweder für bestimmte oder für eine Bandbreite chronischer Erkrankungen entwickelt (z. B. Eaden, Abrams, & Mayberry, 1999; Horne et al., 1999; Moss-Morris et al., 2002; Schmitt et al., 2013). Es gibt jedoch nur begrenzte Möglichkeiten, ein breites Spektrum von Barrieren für die Medikamenteneinnahme ökonomisch zu erfassen. Obwohl einige Messinstrumente bereits verschiedene Einflussfaktoren für die Adhärenz

erfassen, fehlen ihnen einige Barrieren wie z. B. die Qualität der Arzt-Patienten-Interaktion, die sich als relevant herausgestellt haben (Hahn et al., 2008; Müller et al., 2015). Darüber hinaus sind andere Instrumente zur Erfassung von Adhärenz verschiedener Barrieren auf bestimmte Patientengruppen beschränkt (z. B. nur für Patienten mit Bluthochdruck; MUAH: Maastricht Utrecht Adhernece in Hypertension) und ihre Anwendung im Klinikalltag limitiert (Nguyen et al., 2014). Infolgedessen wäre ein möglichst umfassender und ökonomischer Screener, der viele verschiedene Barrieren von Adhärenz erfasst, essentiell für den klinischen Alltag. Dieser Screener könnte für unterschiedliche chronische Erkrankungen verwendet werden und zur Ermittlung des individuellen Risikos eines Patienten, zukünftig non-adhärentes Verhalten zu zeigen, eingesetzt werden. Auf der Basis dieses individuellen Risikoprofils könnte dann für jeden Patienten der spezifische Unterstützungsbedarf für adhärentes Verhalten abgeleitet werden.

Reviews verdeutlichen, dass eine Vielzahl von Faktoren einen Einfluss auf die Adhärenz von Personen mit chronischen Erkrankungen haben (Capoccia, Odegard, & Letassy, 2016; van Dulmen et al., 2007; Vrijens, Antoniou, Burnier, La Sierra, & Volpe, 2017). Die meisten Interventionen zur Verbesserung der Adhärenz zielen darauf ab, die Anwendung der Behandlung zu vereinfachen sowie Erinnerungssysteme zu etablieren und neueste Technologien zu verwenden (Kripalani, Yao, & Haynes, 2007; Schroeder, Fahey, & Ebrahim, 2004). Psychologische Risikofaktoren, die einen Einfluss auf die Adhärenz haben werden oft vernachlässigt (Arlt, Nestoriuc, & Rief, 2017). Diese Risikofaktoren können sowohl in emotionale Faktoren (z. B. Depression, Stress, Angst) als auch kognitive Faktoren (z. B. Überzeugungen über die Behandlung und Medikamenteneinnahme) unterteilt werden. Zudem konnte in weiteren Studien auch der Einfluss von Selbstwirksamkeit (Luszcynska, 2007) oder auch die Qualität der Arzt-Patienten-Interaktion (Janowski, 2013; Kurpas, 2013) nachgewiesen werden. Adhärenz ist ein sehr komplexes Konstrukt, dessen Dimensionen sich wechselseitig beeinflussen können (Sabaté, 2003). Zudem zeigen Patienten auch intra-individuelle Schwankungen in ihrem Adhärenzverhalten (Berg et al., 2014; Wiebe, Baker, Suchy, Stump, & Berg, 2018). Diese werden u. a. durch Unterschiede in den Selbstregulationsfähigkeiten bedingt (Berg et al., 2014). Möglichweise können verschiedene psychologische Risikofaktoren auch die individuellen Gründe für Non-Adhärenz verursachen, die diese Schwankungen erklären.

Daher soll in einem Modell untersucht werden, welche psychologischen Prädiktoren inkrementelle Varianz in einer kurzfristigen (vierwöchigen) Fluktuation der aktuellen gegenüber der vorherigen Adhärenz erklären können. Wenn es in einem Modell gelingt unterschiedliche Risikofaktoren zu identifizieren, die Non-Adhärenz vorhersagen, sollte dies unbedingt für die Entwicklung von Interventionen zur Verbesserung der Adhärenz berücksichtigt werden.

Adhärenz ist ein großes Problem bei Personen, bei denen Diabetes mellitus Typ 2 diagnostiziert wurde (King et al., 2009). Bisher zeigten sich in Metaanalysen nur kleine, kurzfristige Effekte für Interventionen, die zur Verbesserung des Adhärenzverhaltens eingesetzt wurden (Pal et al., 2013). In den letzten Jahren nahm die Anzahl an Online-Programmen kontinuierlich zu (Vandelanotte et al., 2007), jedoch wurden hier oft nur einzelne Outcome-Variablen der Diabetesbehandlung berücksichtigt (Armstrong & Powell, 2008; Glasgow et al., 2003; Noh et al., 2010). Psychologische Interventionen, die auf eine nachhaltige Verhaltensänderung, verbesserte Medikamentenadhärenz sowie Erwartungsveränderungen abzielen, wurden bisher kaum erforscht (McKay et al., 2002). Dabei konnten Studien bereits zeigen, dass Interventionen, die die Erwartungen von Personen mit Diabetes mellitus adressieren, effektiv sind und zu einer Verbesserung im Selbstbehandlungsverhalten führen (Petrie & Broadbent, 2003). Forscher fanden zudem heraus, dass sich die Erwartungen von Patienten mit Hilfe von psychologischen Interventionen beeinflussen lassen (Laferton, 2013). Diese Art der Intervention setzt zum einen an kognitiven Repräsentationen der Erkrankung sowie deren Behandlung an und zum anderen werden emotionale Aspekte der Behandlung aufgegriffen (Heisig et al., 2016). Elemente der kognitiven Verhaltenstherapie bieten dabei eine Vielzahl an Möglichkeiten diese Aspekte zu adressieren.

3.2 Fragestellungen des Dissertationsvorhabens

Basierend auf der bisherigen Forschungsgrundlage zur Non-Adhärenz bei Personen mit chronischen Erkrankungen leiten sich folgende Fragestellungen für die Dissertation ab:

Studie 1: Gibt es psychologische Adhärenz-Risikofaktoren, die bisher in der Literatur vernachlässigt wurden und in zukünftigen Interventionen zur Verbesserung der Adhärenz berücksichtigt werden sollten?

Studie 2: Kann ein Screener entwickelt werden, der unter anderem diese Risikofaktoren erfasst und durch den ein individuelles Risikoprofil erstellt werden kann, um den spezifischen Unterstützungsbedarf für Patienten abzuleiten?

Studie 3: Welche psychologischen Prädiktoren können intra-individuelle Schwankungen in der Adhärenz über vier Wochen vorhersagen?

Studie 4: Verbessert ein Online-Programm das therapiebezogene Adhärenzverhalten bei Personen mit Diabetes mellitus Typ 2?

4 Zusammenfassung der Studien

4.1 Studie 1: Narratives Review zu psychologischen Risikofaktoren für Non-Adhärenz

Warum bisherige Adhärenz-Programme scheiterten: der Fokus auf psychologische Risikofaktoren für Non-Adhärenz.

Arlt, A. D., Nestoriuc, Y., & Rief, W. (2017). Why current drug adherence programs fail: Addressing psychological risk factors of nonadherence. Current Opinion in Psychiatry, 30(5), 326–333. https://doi.org/10.1097/YCO.0000000000000345

Hintergrund. Medikamentenbezogene Non-Adhärenz bei Personen mit chronischen Erkrankungen stellt eine große Herausforderung für das Gesundheitssystem dar. Zwischen 30%-50% der Patienten nehmen ihre Medikamente nicht wie verordnet ein (Cutler & Everett, 2010; Vermeire et al., 2001). Die Gründe für Non-Adhärenz sind individuell und vielseitig (Allemann et al., 2016). Bisherige Adhärenzprogramme haben oftmals unbefriedigende Ergebnisse erbracht, nicht zuletzt, da psychologische Risiken für Non-Adhärenz zu wenig berücksichtigt wurden (Conn et al., 2015; Peterson et al., 2003). Ziel des narrativen Reviews war es, zunächst einen Überblick über psychologische Risikofaktoren für Non-Adhärenz zu geben, die in zukünftigen Adhärenzinterventionen berücksichtigt werden sollen.

Methode. Für das narrative Review wurde die Literatur umfassend via PubMed, PsycINFO, PSYNDEX, PQDT OPEN, OpenGREY, ISI Web of Knowledge und der WHO International Clinical Trials Registry Platform durchsucht. Die Relevanz der psychologischen Adhärenz-Risikofaktoren wurde in einem Expertengremium von klinischen Psychologen beraten (Gremienmitglieder: Prof. Dr. Yvonne Nestoriuc, Prof. Dr. Winfried Rief und M.Sc.-Psych. Antje Arlt).

Ergebnisse. Die bisherige Adhärenzforschung sowie Programme, die zur Verbesserung der Adhärenz eingesetzt wurden, haben nur wenige oder bestimmte Risikofaktoren für non-adhärentes Verhalten berücksichtigt, wie beispielsweise die Komplexität des Medikamentenregimes. Weitere wichtige Risikofaktoren wurden vernachlässigt oder nicht in die entsprechenden Programme implementiert. Es zeigte sich Evidenz dafür, dass die Qualität der Arzt-Patienten-Interaktion einen signifikanten Einfluss auf die medikamentöse Adhärenz hat. Weitere Risikofaktoren wie das bisherige Adhärenzverhalten, eine geringe Akzeptanz der eigenen Erkrankung gegenüber, Überzeugungen über die Erkrankung sowie der Behandlung und die Angst vor potenziellen Nebenwirkungen eines Medikamentes wurden in bisherigen Adhärenzprogrammen zu wenig berücksichtigt. Zudem sollten die Interventionen an die kognitiven Einschränkungen sowie Komorbiditäten wie z. B. depressive Symptome angepasst werden.

Schlussfolgerung. Die bisherige Forschung zu Determinanten medikamentöser Adhärenz sowie adhärenzsteigernden Interventionen vernachlässigt psychologische Risikofaktoren für Non-Adhärenz. Diese sollten in zukünftigen Studien unbedingt berücksichtigt und individuell an die Bedürfnisse der Patienten angepasst werden. Dies könnte ein potenzieller Weg sein, Interventionen zu entwickeln und zu evaluieren, um die Adhärenz von Personen mit unterschiedlichen Erkrankungen zu verbessern.

4.2 Studie 2: Die Entwicklung eines Screeners zur Erfassung von psychologischen Risikofaktoren

Wird dieser Patient non-adhärent sein? Die Vorhersage der Non-Adhärenz bei verschiedenen chronischen Erkrankungen mit dem Adhärenz-Risko-Profil (AdRisk).

Arlt, A., Schomburg, J., Rinn, A., & Rief W. (submitted). Will this Patient become Non-Adherent? Predicting Non-Adherence in Chronic Diseases with the Adherence Risk Profile (AdRisk). Manuscript submitted for publication in *Journal of Behavioral Medicine*.

Hintergrund. Medikamentenbezogene Non-Adhärenz ist ein weitverbreitetes Problem in der Behandlung von chronischen Erkrankungen (Osterberg & Blaschke, 2005). Adhärenzraten, die in der Literatur berichtet werden, variieren zwischen 30%-50% (Cutler & Everett, 2010; Vermeire et al., 2001). Die Folgen von mangelnder Adhärenz sind gravierend. Denn neben dem schlechteren Gesundheitszustand des Patienten entstehen dem Gesundheitssystem immense Kosten (Sabaté, 2003). Es wurden bereits verschiedenste einzelne Einflussfaktoren auf Adhärenz untersucht (Brawley & Culos-Reed, 2000; Osterberg & Blaschke, 2005; Vermeire et al., 2001), zu deren Erfassung auch Instrumente entwickelt wurden. Diese ermöglichten bisher jedoch keine ausreichend umfassende und ökonomische Erfassung von verschiedenen Barrieren für Adhärenz im Klinikalltag. In dieser Studie wurde ein Inventar validiert, das für Patienten mit unterschiedlichen chronischen körperlichen Erkrankungen eingesetzt werden kann. Durch die ökonomische Erfassung möglichst vieler mit Adhärenz assoziierter Variablen soll ein Risiko-Profil des Patienten erstellt werden, aus dem der individuelle Unterstützungsbedarf für adhärentes Verhalten abgeleitet werden kann.

Methode. Es wurden Daten von 677 Personen mit einer chronischen Erkrankung online erhoben. Die Teilnehmer berichteten die Diagnose einer der folgenden 6 Erkrankungsarten: Diabetes mellitus Typ 2, Bluthochdruck, Epilepsie, chronisch obstruktive Lungenerkrankung

(englisch: chronic obstructive pulmonary disease; COPD), rheumatoide Arthritis oder Morbus Crohn und deren medikamentöse Behandlung. Rekrutiert wurden die Personen über Flyer und Aushänge in Arztpraxen, Apotheken und anderen öffentlichen Orten in Marburg und Gießen, Facebook-Gruppen für Betroffene, Newsletter, Zeitschriften, Websites von Vereinen und Patientenverbänden. Es wurden Standard-Itemanalysen durchgeführt sowie interne Konsistenz und Test-Retest-Reliabilität berechnet. Um die Faktorenstruktur zu untersuchen, wurde die Gesamtstichprobe in zwei Teilstichproben eingeteilt. Eine exploratorische Maximum-Likelihood Faktorenanalyse (Varimax-Rotation) wurde mit der Teilstichprobe A und eine konfirmatorische Faktorenanalyse mit der Teilstichprobe B durchgeführt. Zur Bestimmung der Konstruktvalidität wurde die Assoziation der zwei Gesamtwerte (ART = AdRisk Total, Summenwert; BT = Barriers Total, Anzahl der Adhärenz-Barrieren), sowie der vier Subskalen des Inventars mit Adhärenz (gemessen mit dem MARS-D) bestimmt.

Ergebnisse. Der AdRisk zeigte gute psychometrische Charakteristika. Der Screener hatte eine gute interne Konsistenz mit $\alpha = .82$ (Cronbach) und einer Test-Retest-Reliabilität von .83. Mittels multipler hierarchischer Regressionen konnte die positive Assoziation der zwei AdRisk-Gesamtwerte sowie der vier Subskalen nachgewiesen werden. Die Ergebnisse zeigen somit eine gute Konstruktvalidität. Die exploratorische Faktorenanalyse ließ auf eine Vier-Faktoren-Struktur schließen, die 61% der gesamten Item-Varianz aufklärte. Diese Struktur wurde durch die konfirmatorische Faktorenanalyse bestätigt.

Diskussion. Der AdRisk zeigte zufriedenstellende psychometrische Charakteristika. Er kann als ein ökonomisches Screening-Instrument für unterschiedliche, chronische körperliche Erkrankungen im klinischen Alltag eingesetzt werden. Durch die breite Erfassung von unterschiedlichen Barrieren kann der individuelle Unterstützungsbedarf für jeden Patienten abgeleitet werden.

4.3 Studie 3: Überprüfung eines Modells zur Vorhersage von intra-individuellen Schwankungen von Adhärenz nach vier Wochen

Welche psychologischen Prädiktoren können kurzfristige Schwankungen der Medikamentenadhärenz bei verschiedenen chronischen Erkrankungen erklären?

Arlt, A., Wilhelm, M., Euteneuer, F., & Rief W. (submitted). Psychological predictors of fluctuation in medication adherence in various chronic conditions. Manuscript submitted for publication in *Health Psychology*.

Hintergrund. Non-Adhärenz ist ein persistierendes Problem bei verschiedenen chronischen Erkrankungen (van Dulmen et al., 2007). Neben den Belastungen und gesundheitlichen Einschränkungen führt Non-Adhärenz zu immensen Kosten für das Gesundheitssystem (Osterberg & Blaschke, 2005; Sabaté, 2003). Bisher wurden psychologische Risikofaktoren oft vernachlässigt. Daher war es das Ziel dieser Studie, psychologische Prädiktoren zu identifizieren, die über bisherige Adhärenz hinaus Varianz in intraindividueller Adhärenz-Fluktuation über vier Wochen erklären.

Methode. Für diese Sekundäranalyse wurden Daten aus der Validierungsstudie des „AdRisk“ verwendet. 677 Personen mit einer chronischen Erkrankung (Diabetes mellitus Typ 2, Bluthochdruck, Epilepsie, COPD, rheumatoide Arthritis) nahmen an einer Onlinebefragung teil, die die Qualität der Arzt-Patienten-Interaktion, Zufriedenheit mit Informationen über die Medikation, Angst, Depression, Stress, Selbstwirksamkeit in Bezug auf die Medikamenteneinnahme, Überzeugungen über die Behandlung und Medikation, Krankheitswahrnehmung und Krankheitsakzeptanz mittels etablierter Fragebögen erfasste. Zudem wurden die aktuelle Adhärenz sowie das Adhärenzverhalten in der Vergangenheit als ein stabiles Verhaltensmaß erhoben. 400 Patienten gaben nach vier Wochen erneut eine Einschätzung zu ihrer aktuellen Adhärenz ab. Die Daten wurden mittels Pfadanalysen analysiert.

Ergebnisse. Alter (standardisierter Koeffizient β = .06, *p* = .01), aktuelle Adhärenz (β = .24, *p* < 0.01), die Qualität der Arzt-Patienten-Interaktion (β = .08, *p* < .01), Stress (β = .16, *p* < .01), Selbstwirksamkeit in Bezug auf die Medikamenteneinnahme (β = .25, *p* = .01) und Adhärenzverhalten in der Vergangenheit (β = -.29, *p* < .01) waren mit Adhärenz positiv assoziiert. Während die Zufriedenheit mit Informationen über die Medikation (β = -.08, *p* < .01) und Angst (β = -.29, *p* < .01) negativ mit Adhärenz nach vier Wochen assoziiert war.

Diskussion. Zusammenfassend konnte gezeigt werden, dass einige psychologische Risikofaktoren intra-individuelle Schwankungen von Non-Adhärenz nach 4 Wochen vorhersagen können. Insbesondere die Qualität der Arzt-Patienten-Interaktion, die Selbstwirksamkeit, Zufriedenheit mit Informationen über die Medikation und Angst sind dabei bedeutsam.

4.4 Studie 4: Studienprotokoll einer Online-Intervention zur Verbesserung des Adhärenzverhaltens

Erwartungsfokussierte Online-Intervention zur Optimierung der Adhärenz bei Patienten mit -Diabetes mellitus Typ 2: Studienprotokoll einer randomisierten kontrollierten Studie.

Arlt, A., Schomburg, J., Meyer B., Jacob, G., Rief W., & Nestoriuc, Y. (submitted). Expectation-focused online intervention to optimise adherence in patients with type-II diabetes mellitus: Protocol of a randomised controlled trial. Manuscript submitted for publication in *BMC Endocrine Disorders*.

Hintergrund. Die Behandlung von Diabetes mellitus Typ 2 stellt eine große Herausforderung für das deutsche Gesundheitssystem dar. Die Prävalenzrate liegt in Deutschland derzeit bei etwa 9.9% und steigt stetig (Jacobs & Rathmann, 2018). Das Adhärenzverhalten umfasst eine adäquate physische Aktivität, ein gesundes Ernährungsverhalten, die regelmäßige Kontrolle des Blutzuckers und die regelmäßige medikamentöse Behandlung (Schmitt et al., 2013). Adhärenzraten bezüglich verschiedener Aspekte des Selbstbehandlungsverhaltens variieren stark (Cramer, 2004). Es zeigt sich Evidenz dafür, dass Online-Programme das Selbstmanagement von Personen mit Diabetes mellitus Typ 2 verbessern können (Ramadas et al., 2011). Allerdings gibt es bisher nur uneindeutige Befunde bezüglich der Relevanz verschiedener Aspekte des Selbstbehandlungsverhaltens (Davies et al., 2012; Ismail et al., 2004). Daher soll in dieser randomisiert kontrollierten Studie die Wirksamkeit eines psychologischen Online-Programms auf das Adhärenzverhalten überprüft werden. Zudem soll geklärt werden, ob die Erwartungen an die Behandlung und die Erkrankung einen mediierenden Effekt haben. Das Studienprotokoll soll hier dargestellt werden.

Methode/Design. Insgesamt sollen 290 Personen mit Diabetes mellitus Typ 2 eingeschlossen und zufällig einem diabetesspezifischen Online-Programm mit dem Fokus auf Erwartungen (Covivio), einer aktiven Kontrollgruppe mit einem Online-Entspannungs-Programm (Relaxio) oder einer Wartekontrollgruppe zugewiesen werden. Die Teilnehmer werden über Arztpraxen, diabetische Schwerpunktkliniken, das Internet sowie Anzeigen und Flyer rekrutiert. Einschlusskriterien sind: das Mindestalter von 18 Jahren, die Diagnose Diabetes mellitus Typ 2, Defizite im Selbstmanagementverhalten (gemessen durch den Diabetes Self Management Questionnaire Schmitt et al., 2013 DSMQ-R: Cut-off 7.5), die regelmäßige Kontrolle des Hämoglobin-Wertes (HbA1c), das Fehlen von schweren psychischen Störungen und der Besitz eines Internetzuganges. Das primäre Outcome der Studie ist das Adhärenzverhalten, das über den subjektiven Selbstbericht in Bezug auf die Medikamenteneinnahme, das Bewegungsverhalten und der Ernährungsgewohnheiten erfasst wird. Als sekundäre Parameter werden die Veränderung des Hämoglobin-Wertes (HbA1c), Folgeerkrankungen, der Body-Maß-Index (BMI), die physische Aktivität, psychische Symptome wie Depressivität, Ängstlichkeit, gesundheitsbezogene Lebensqualität sowie das Ausmaß an Somatisierung erfasst. Die Fragebögen werden online zum Baseline-Zeitpunkt sowie nach zwei, drei und sechs Monaten untersucht. Die Erwartungen an die Behandlung als auch an die Erkrankungen sollen als Mediatoren mit in die Analyse aufgenommen werden.

Diskussion. Erwartungsfokussierte Online-Programme könnten bei Personen mit Diabetes mellitus Typ 2 ein potenzieller Weg sein, um ihr Adhärenzverhalten zu verbessern und die Versorgung der Patienten zu ergänzen. Die Ergebnisse werden wichtige Erkenntnisse zu psychologisch evidenzbasierten Online-Programmen liefern und möglicherweise das bereits vorhandene Repertoire an wirksamen Behandlungsoptionen erweitern mit dem Ziel, die Adhärenz in dieser Patientengruppe zu verbessern.

5 Zusammenfassende Diskussion und Ausblick

Für das narrative Review (Studie 1) wurde die Relevanz der psychologischen Adhärenz-Risikofaktoren in einem Expertengremium beraten und hinsichtlich der klinischen Relevanz diskutiert. Es zeigte sich, dass wichtige Risikofaktoren bisher vernachlässigt oder nicht in die entsprechenden Programme implementiert wurden. Die Qualität der Arzt-Patienten-Interaktion, das bisherige Adhärenzverhalten, eine geringe Akzeptanz der eigenen Erkrankung gegenüber, Überzeugungen über die Erkrankung sowie der Behandlung und die Angst vor potenziellen Nebenwirkungen eines Medikamentes wurden in bisherigen Adhärenzprogrammen zu wenig berücksichtigt. Weiterhin sollten Interventionen an die kognitive Einschränkungen sowie Komorbiditäten wie z. B. depressive Symptome individuell an die Behandlung angepasst werden. Die Entwicklung von Interventionen, die den Fokus auf psychologische Risikofaktoren legen, könnte ein vielversprechender Weg sein, um die Adhärenz von Personen mit unterschiedlichen Erkrankungen zu verbessern.

Der AdRisk (Studie 2) ist eines der ersten Screening-Instrumente, mit dem ein breites Spektrum an Barrieren erfasst werden kann, die einen Einfluss auf die Adhärenz bei Personen mit unterschiedlichen chronischen körperlichen Erkrankungen haben könnten. Der AdRisk zeigte gute psychometrische Charakteristika. Der Screener hatte eine gute interne Konsistenz mit α=.82 (Cronbach) und einer Test-Retest Reliabilität von α=.83 (Cronbach). Mittels multipler hierarchischer Regressionen konnte die positive Assoziation der zwei AdRisk-Gesamtwerte sowie der vier Subskalen nachgewiesen werden. Die Ergebnisse verweisen somit auf eine gute Konstruktvalidität. Die ML Faktorenanalyse extrahierte vier Faktoren, die 61% der gesamten Varianz aufklärten. Diese Struktur wurde durch die CFA bestätigt.

Mittels Pfadanalysen (Studie 3) konnte überprüft werden, welche psychologischen Prädiktoren die inkrementelle Varianz in einer kurzfristigen (vierwöchigen) Fluktuation der aktuellen gegenüber der vorherigen Adhärenz erklären können. In der Studie konnte eine positive Assoziation von Alter, der Qualität der Arzt-Patienten-Interaktion, Stress und die Selbstwirksamkeit in Bezug auf die Medikamenteneinnahme und Adhärenz gezeigt werden. Für die Zufriedenheit mit Wissen über die Medikation und die Ausprägung von Angst konnte

ein negativer Zusammenhang gezeigt werden. Somit konnten einige psychologische Risikofaktoren, intra-individuelle Schwankungen für eine Non-Adhärenz nach 4 Wochen vorhersagen, die über die erklärte Varianz von der vorherigen Medikamenteneinhaltung hinausgehen.

Ebenfalls wurde das Studienprotokoll (Studie 4) einer Online-Intervention für Personen mit Diabetes mellitus Typ 2 dargestellt. Das Ziel der Studie war es, das Online-Programm „Covivio“ in Hinblick auf das Selbstbehandlungsverhalten sowie der Medikamentenadhärenz von Personen mit Diabetes mellitus Typ 2 zu evaluieren. Der Gesamtwert des DSMQ-R (Schmitt et al., 2013) (Primäres Outcome) sollte in der Interventionsgruppe unmittelbar nach der Intervention im Vergleich zu der Gruppe mit der Entspannungsintervention „Relaxio“ und der Wartekontrollgruppe, signifikant höher sein. Des Weiteren sollte überprüft werden, ob dieser Effekt über die Zeit stabil ist (drei- und sechsmonatiges Follow-up) und ob die Erwartungen der Patienten an die Krankheit und die Behandlung einen mediierenden Effekt auf das Selbstbehandlungsverhalten und die medikamentöse Adhärenz haben.

5.1 Einschränkungen

In Studie 2 war die Teilnahme an der Studie freiwillig und viele Teilnehmer wurden über soziale Netzwerkgruppen oder Patientenorganisationen rekrutiert. Dies könnte zu einem Deckeneffekt beigetragen haben, sodass Personen, die ein großes Interesse an wissenschaftlichen Studien zeigen, bereits eine höhere medikamentenbezogene Adhärenz haben. Da es sich um eine Online-Studie handelte, wurden möglicherweise ältere Personen mit chronischen Erkrankungen zu wenig erfasst. In Studien zeigt sich, dass insbesondere bei dieser Population die Adhärenz problematisch ist (Gellad, Grenard, & Marcum, 2011). Dies könnte ebenfalls zu einer reduzierten Varianz und zum Deckeneffekt beigetragen haben. Zweitens wurde in der Studie die Adhärenz mittels Selbstbeobachtungsfragebögen erfasst und keine objektiven Verfahren zur Erfassung der Medikamenteneinnahme verwendet (Lam & Fresco, 2015). Verzerrungen, die absichtlich oder auch unabsichtlich entstanden sind, wurden nicht weiter berücksichtigt. Die Studie enthielt keine Skala für soziale

Erwünschtheit, die Hinweise auf eine potenzielle Verzerrung geben könnten (Stirratt et al., 2015). Drittens sollte der AdRisk noch hinsichtlich der Sensitivität und der Spezifität untersucht werden. Mit Hilfe eines theoretisch begründeten Cut-off-Wertes könnten die einzelnen Items hinsichtlich der diskriminativen Validität analysiert werden. So könnte nachgewiesen werden, ab welchem Punkt sich die jeweiligen Items zwischen adhärenten und nicht-adhärenten Personen unterscheiden.

In der Studie 3 wurde eine Sekundäranalyse der Daten durchgeführt, die im Rahmen der Validierung des AdRisk erhoben wurden. Es handelte sich, gemessen an dem MARS-Gesamtwert, um eine adhärente Stichprobe, die somit möglicherweise nicht repräsentativ für die gesamte Patientenpopulation abgebildet werden konnte. Daher wäre es sinnvoll in einer nachfolgenden Studie die Ergebnisse mit einer Patientenstichprobe zu replizieren, die in Arztpraxen oder Fachkliniken rekrutiert wurde. Die Daten wurden online erhoben, daher konnten die Einschlusskriterien wie die für die Studie relevante Diagnose, verschriebene Medikamente, Behandlungsdauer oder Komorbidität und Adhärenz nicht extern verifiziert werden. Eine objektive Messung der Medikamenteneinnahme sowie ein Fragebogen, der die soziale Erwünschtheit erfasst, sollten in Zukunft zur Bestätigung unserer Ergebnisse herangezogen werden. In Bezug auf die Pfadanalysen ist anzumerken, dass das modifizierte Modell vorab nicht an einem Teildatensatz getestet wurde und daher sollte er zumindest an einem neuen Datensatz überprüft werden. Zudem ist die Anzahl von manifesten Variablen, die in das Modell mitaufgenommen wurden, als kritisch zu betrachten. Allerdings ist die Stichprobe mit 677 Teilnehmenden recht groß und auch die Modellfit-Indices können als zufriedenstellend betrachtet werden.

In Studie 4 kann zunächst positiv hervorgehoben werden, dass es sich um ein randomisiert-kontrolliertes Studiendesign handelt. Zudem werden zwei Follow-up Messungen zur Überprüfung der Langzeiteffektivität durchgeführt. Für die Erfassung der Variablen werden nur Messinstrumente mit akzeptablen bis exzellenten internen Konsistenzen eingesetzt. Des Weitern ist dies die erste Studie bei der die Erwartungen an die Behandlung modifiziert wurden, um das Adhärenzverhalten bei Personen mit Diabetes mellitus Typ 2 zu verbessern. Einige Personen mit Diabetes, insbesondere solche mit Diabetes Typ 2, sind älter und haben möglicherweise einen eingeschränkten Zugang zum Internet, dies könnte zu Einschränkungen in der Repräsentativität führen. Die

Studienteilnahme ist freiwillig, dies könnte zu einem Deckeneffekt führen. Eine systematische Überprüfung ergab, dass Personen mit Diabetes, die sehr motiviert sind und eine gute Blutzuckerkontrolle zeigen, eher in diabetesspezifischen Online-Portalen aktiv sind, als solche mit einer schlechten Kontrolle (Amante, Hogan, Pagoto, & English, 2014). Des Weiteren können negative Vorerfahrungen mit Online-Programmen ebenfalls einen Einfluss haben (Amante et al., 2014). Für die Evaluation können leider keine Rückschlüsse auf die Teile des Online-Programms gezogen werden, die besonders wichtig für die Veränderung von Adhärenz sind. Zudem muss die Selbstauskunft der Patienten mit Diabetes kritisch diskutiert werden. So kann die Tendenz zu sozialer Erwünschtheit, die als Anpassung des eigenen Verhaltens oder der Beschreibung der eigenen Person an soziale Normen definiert wird, zu einer Verzerrung führen (Gollwitzer & Jäger, 2014). Dies verringert wiederum die Validität der Messung. Dieser Aspekt ist bei der Erfassung von Adhärenzverhalten von besonderer Bedeutung, da die Adhärenz in vielen Studien durch den Selbstbericht überschätzt wird (Shi et al., 2010).

5.2 Perspektiven für Forschung und Praxis

Die vorliegende Dissertation bietet einige Ansatzpunkte für weiterführende Forschung.

Studie 1: Im nächsten Schritt sollten Interventionen entwickelt und evaluiert werden, deren Fokus auf psychologischen Risikofaktoren liegt. Es gibt bereits erste Hinweise, dass psychologische Interventionen die Adhärenz von Personen mit chronischen Erkrankungen verbessern können (Peterson et al., 2003; Simpson et al., 2006). Wenn nachgewiesen werden kann, dass psychologische Aspekte die Versorgung maßgeblich verbessern können, sollte dies unbedingt in die Routineversorgung aufgenommen und in die Leitlinien zur Behandlung dokumentiert werden.

Studie 2: Es zeigt sich Evidenz dafür, dass einzelne Items zur ökonomischen Erfassung relevanter Barrieren für Non-Adhärenz eingesetzt werden können. Angesichts der begrenzten Zeit, die Kliniker mit ihren Patienten zur Verfügung haben, ist die ökonomische Erfassung von herausragender Bedeutung und könnte daher auch regelmäßig zur Erfassung eingesetzt werden. In der vorliegenden Studie wurden Risikofaktoren berücksichtigt, die

bisher in der Forschung vernachlässigt wurden. So konnten beispielsweise das generelle Adhärenzverhalten in der Vergangenheit und die Akzeptanz, eine chronische Erkrankung zu haben, als mögliche Risikofaktoren identifiziert werden. Dies sollte in zukünftigen Studien unbedingt berücksichtigt werden. Zudem könnte in einer nachfolgenden Studie die Rekrutierung der Personen über Arztpraxen und Kliniken erfolgen. Dies könnte dazu führen, dass auch Personen mit einer niedrigeren Adhärenz an der Studie teilnehmen und so die Repräsentativität der Population erhöhen. Möglicherweise gibt es Unterschiede zwischen den Erkrankungsgruppen (Diabetes mellitus Typ 2, Bluthochdruck, Epilepsie, chronisch obstruktive Lungenerkrankung). Dies könnte auch für weitere Analysen berücksichtigt werden oder als Kovariate mit analysiert werden.

Studie 3: Um die Adhärenz bei Patienten mit chronischen Erkrankungen zu verbessern, ist es wichtig, zunächst zwischen unveränderbaren (z.B. Alter) und modifizierbaren Faktoren (z. B. Überzeugungen über Medikamente) zu unterscheiden und Interventionen daran individuell anzupassen (Allemann et al., 2016). Ergänzend dazu sollte unbedingt berücksichtigt werden, dass Adhärenz auch intra-individuellen Schwankungen unterliegt, die von Faktoren wie der Qualität der Arzt-Patienten-Interaktion, der Selbstwirksamkeit, der Zufriedenheit mit Informationen über die Medikation und Angst zusammenhängt. Für den klinischen Alltag ist das von großer Bedeutung, da durch den aktive Einbezug der Patienten, das Selbstwirksamkeitserleben gefördert wird (Colbert, Sereika, & Erlen, 2013; Luszczynska, Sarkar, & Knoll, 2007) und im gemeinsamen Gespräch das Wissen über die Erkrankung und die medikamentöse Behandlung verbessert werden (Bourbeau & Bartlett, 2008; Horne, Hankins, & Jenkins, 2001). Zudem sollten Behandler geschult werden Komorbiditäten wie z. B. Angsterkrankungen zu erkennen und entsprechende Behandlungen einzuleiten. Dies könnte dann folglich zu einer Verbesserung der Adhärenz führen, Folgeerkrankungen verhindern und die Lebensqualität verbessern (Dimatteo et al., 2002).

Studie 4: Bisher sind Programme zur Verbesserung des Adhärenzverhaltens nur auf Englisch verfügbar (Glasgow et al., 2010). Die Implementierung für den deutschsprachigen Raum ist jedoch dringend notwendig. Darüber hinaus sollte dringend untersucht werden, welche langfristigen Effekte durch die Programmnutzung erzielt werden können. Zudem sollten auch die spezifischen Wirkkomponenten erfasst und analysiert werden. Möglicherweise könnte es in Abhängigkeit der Erkrankungsdauer Unterschiede zwischen

Personen geben. Zukünftige Forschung sollte die Wirkmechanismen für Veränderung im Adhärenzverhalten untersuchen. Aktuelle Forschungsergebnisse zeigen (Rief & Glombiewski, 2016), dass durch verhaltenstherapeutische Strategien die Erwartungen an die Behandlung und die Erkrankung optimiert werden können und gezielt zur Verbesserung des Adhärenzverhaltens eingesetzt werden sollten. Durch den Einsatz von Online-Programmen können Kosten für das Gesundheitssystem gesenkt werden, hierfür sollten Kosten-Nutzen-Analysen durchgeführt werden.

5.3 Fazit

Mit der vorliegenden Arbeit ist es gelungen, die Bedeutung psychologischer Aspekte zur Verbesserung von Adhärenz bei Personen mit chronischen Erkrankungen herauszustellen. Dabei konnte eine Vielzahl von psychologischen Risikofaktoren für Non-Adhärenz identifiziert werden, die in zukünftigen Adhärenzprogrammen berücksichtigt werden sollen und so die Adhärenz von Personen mit chronischen Erkrankungen verbessern können. Es konnte ein „Adhärenz Risikoprofil Screener“ (AdRisk) entwickelt werden, der als ein ökonomisches Instrument zur breiten Erfassung von unterschiedlichen Barrieren und für unterschiedliche chronische körperliche Erkrankungen im klinischen Alltag eingesetzt werden kann. Zudem konnten in einem längsschnittlichen Design einige psychologische Risikofaktoren identifiziert werden, die intra-individuelle Schwankungen von Non-Adhärenz nach 4 Wochen vorhersagen können. Insbesondere die Qualität der Arzt-Patienten-Interaktion, die Selbstwirksamkeit in Bezug auf die Medikamenteneinnahme, Zufriedenheit mit Informationen über die Medikation und Angst sind dabei besonders bedeutsam. Abschließend wurde ein Studienprotokoll verfasst über eine Studie, indem ein psychologisches Online-Programm für Personen mit Diabetes evaluiert werden soll. Zudem soll geklärt werden, ob die Erwartungen an die Behandlung und die Erkrankung einen mediierenden Effekt haben.

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Appendix

A. Studien

A. 1 Studie 1

Arlt, A. D., Nestoriuc, Y., & Rief, W. (2017). Why current drug adherence programs fail: Addressing psychological risk factors of nonadherence. Current Opinion in Psychiatry, 30(5), 326–333. https://doi.org/10.1097/YCO.0000000000000345

REVIEW

Why current drug adherence programs fail: addressing psychological risk factors of nonadherence

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Purpose of review
To provide an overview of a selection of largely neglected psychological risk factors for nonadherence, and to offer new approaches to improve medication adherence.

Recent findings
Current adherence research and intervention programs focus on a few risk factors for nonadherence, such as complexity of the drug regimen. In addition, other important risk factors of nonadherence are neglected or insufficiently addressed. There is good evidence for the significant role of the quality of the patient–healthcare provider relationship. Other risk factors like the individual history of nonadherence, the lack of acceptance of having a treatable disorder, fear of side-effects, comorbid depression, and cognitive impairment have been broadly neglected in adherence programs, although they offer a powerful key to improve adherence-oriented interventions.

Summary
Current research on determinants of nonadherence has focused on a few risk factors, while neglecting crucial psychological predictors of nonadherence. The personalized consideration of a multiplicity of risk factors offers a new basis for the development and evaluation of interventions to better promote adherence.

Keywords
cognitive impairment, compliance, depression, doctor–patient relationship, fear of side-effects, illness acceptance, nonadherence

INTRODUCTION

Medication nonadherence in persons with chronic diseases remains a major challenge for the healthcare system. The WHO defines adherence as 'the extent to which the person's behavior – taking medication, following a diet, and/or executing lifestyle changes – corresponds with the agreed recommendations from a healthcare provider [1]. This definition illustrates the importance of the active interaction of the person with a chronic disease and the healthcare provider [2].

During the last four decades, there have been many attempts to develop instruments to measure adherence, to understand the factors that trigger nonadherence, and to generate interventions, which promote adherence. This body of research has yielded inconsistent results. Up to now, there is no 'gold standard' for identifying individual reasons for nonadherence [3], there is a multiplicity of factors that influence adherence [4▪], and the effects of interventions to improve patients' adherence and other health-related outcomes are small or inconsistent [5].

Despite these efforts, adherence has not lost its topicality. Still 25–50% of those diagnosed with a chronic disease do not take their medication as prescribed, and this range has been relatively stable over the past years [6,7]. Benefit from the prescribed treatment is hence limited for a large proportion of patients, namely those with incomplete adherence. Although a guideline-based medication treatment and the establishment of health-promoting

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KEY POINTS

- Nonadherence is a crucial and costly problem in healthcare systems.
- Current approaches to improve medication adherence neglect essential psychological risk factors for nonadherence.
- Nonadherence programs can be further improved by focusing on aspects such as fear of side-effects, illness acceptance, beliefs about medications, doctor–patient relationship, cognitive impairment, and comorbid depression.

behaviors will improve the quality of life, prevent secondary diseases, and reduce mortality rates of many patients, nonadherence limits the potential of medical interventions in both acute and chronic disorders [8]. Furthermore, the immense costs of the healthcare system that evolve from nonadherence could be reduced [1].

In a pragmatic review, Allemann *et al.* [4▪] grouped interventions for enhancing medical adherence into 11 categories: knowledge, skills, social cohesion and identity, beliefs about abilities, beliefs about consequences, intentions, memory, attention and decision-making processes, environmental contexts and resources, social influences, and emotion and behavioral regulation. In addition, the reported interventions in respect of the aforementioned 11 categories yielded inconsistent results. That is further confirmed by meta-analytic results demonstrating no overall benefit of interventions aimed at enhancing adherence [9].

To summarize, the results of interventions to improve adherence have been mixed. Interventions that were associated with adherence typically did not improve other health outcomes such as quality of life, biomarkers, healthcare utilization, and satisfaction [10].

INTEGRATIVE APPROACHES

The characteristics of adherence are complex. In addition, adherence can be divided into three phases: the initiation of the treatment, the implementation of the individual treatment concept, and the discontinuation of treatment [11].

The WHO proposes five dimensions of adherence: factors of the health system, socioeconomic factors, patient-related factors, therapy-related factors, and factors of the disease [1]. Nonadherence is usually multicausal. The WHO explicitly points out that it is a dynamic process that is subject to temporal fluctuations over the course of the disease. Nevertheless, the WHO dimensions used to classify interventions and patient responses lack the refinement necessary to provide a meaningful orientation [4▪].

One aspect that is often discussed is the lack of a theory as a basis to develop interventions to promote adherence [12]. The health belief model [13] and the common sense model of self-regulation have often been used and have been adapted for this purpose [14,15]. Also the transtheoretical model has been discussed to develop adherence interventions [16].

The necessity-concerns model [15] is an adherence-specific model. It proposes that adherence is the result of an individual decision-making process, the determinants of which are beliefs about the necessity of taking the medication and concerns about the potential adverse consequences of taking it. These determinants are influenced by intentional (e.g. lack of motivation) and unintentional (e.g. lack of resources and skills) reasons for nonadherence [17]. These parameters, which are sometimes contradictory, are processed in the individual and result in the individual degree of adherence.

Up to now, there are some well established factors – for example medical and socioeconomic characteristics of the patient [18], comprehension of the treatment necessity [19▪], and shared decision-making [20] – which influence adherence. In addition, there are further motivational aspects that influence the adherence of individuals who are diagnosed with a chronic disease. Therefore, the purpose of this narrative review is to provide an overview of a selection of neglected risk factors for nonadherence (Fig. 1) and corresponding interventions to improve adherence.

RISK FACTORS OF NONADHERENCE

Complexity of the drug regimen

The complexity of the drug regimen is associated with nonadherence in persons with chronic diseases, in the elderly, and in multimorbid patients and is associated with reduced quality of life, less use of medical services, and an increase in caregiver burden [21].

Relevant new aspects are the intrusiveness, the extent of inconvenience, and the degree of attention required to incorporate a new routine or procedure into daily life [22]. Moreover, the number of medications, the dosage frequency, and the prescribed dosage forms can be barriers to adherent behavior [22,23]. Pill size or bitter taste of drugs can further contribute to nonadherence [24,25]. The medication regimen complexity index (MRCI)

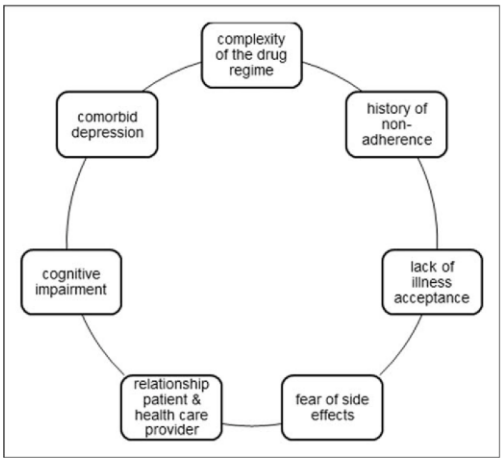

FIGURE 1. Risk factors for nonadherence.

is a frequently used reliable and valid tool to register the complexity of the drug regimen [26].

An individually adapted drug regimen should consider the daily habits of the patient to promote adherence [27,28] and potential simplifications of the dosing system [29]. To reduce the liability from pill burdens, the frequency of dosing should be reduced [29] and combination pills should be prescribed whenever medically possible [9].

Ryan *et al.* [29] propose that changing the medication formulation to enhance efficacy and reduce side-effects may have a positive effect on adherence. Medication formulation change, in particular in generic medication, seems to be associated with reduced subjective and objective measures of medication effectiveness and increased side-effects [30]. The impact of the brand name or a generic labeling of the medication has been shown in an experimental study with a counterbalanced design [31]. Participants in the brand group reported a higher rate of pain reduction and fewer side-effects in the verum and in the placebo group in comparison to the generic group.

Mobile technologies (mHealth) are increasingly being used in healthcare to support patients. Reminders such as phone calls, text messages, interactive voice response (IVR) systems, pagers, and video telephone calls can remind persons with a chronic disease to take their medication [32]. The SMS service was the most common mHealth intervention (40.2%) in promoting adherence [33].

In addition, the clinical effects of commonly used modern healthcare information technology-based interventions are still overall judged as moderate [34].

History of nonadherence

Past behaviors concerning medication intake are a valid predictor for current medication intake both in the general population and in populations with chronic diseases [35]. The Rief adherence index (RAI) is a reliable and valid tool to assess past medication nonadherence, and allows prediction of current medication adherence [35].

A current study involving a population of persons with type 2 diabetes confirms that health behaviors are stronger predictors for health outcomes than treatment beliefs [36▪]. Adherence to the treatment regimen or to the general medical advice, measured by self-report, consistently predicts both glycemic control and cardiovascular risk factors.

Past behavior concerning medication intake is a valid predictor for adherence during subsequent treatment. Further research is needed to investigate this psychological risk factor of nonadherence.

Illness acceptance

It seems true that acceptance of suffering from a clinical condition that needs medical treatment is a prerequisite for adherence. Illness acceptance can be considered as a result of the subjective illness perception and disease representation of a person with a chronic disease (self-regulation model) [37]. Although higher illness acceptance leads to more active coping, lower illness acceptance is associated with a lower quality of life [38] and nonadherence [39].

In addition, there is a lack of instruments to measure the degree of illness acceptance for chronic diseases. The Chronic Illness Acceptance Questionnaire [40] is an adapted version of the Chronic Pain Acceptance Questionnaire [41], showing only an adequate to good fit to the data of a survey. Schmitt *et al.* [42] validated the Diabetes Acceptance Questionnaire. Nonacceptance of diabetes mellitus was significantly associated with less active coping (−0.37), reduced self-care (−0.43), a higher HbA1c level (0.31), as well as more diabetes-specific distress (0.53) and more depressive symptoms (0.36).

In general, there are limited opportunities to recognize insufficient acceptance and provide appropriate interventions for patients. Sharpe and Curran [43] suggest the following intervention strategies: identification of disease-related persuasions, resource orientation, focusing on short-term, medium-term, and long-term goals and identifying the benefits of the disease. Furthermore, acceptance-based treatments like acceptance and commitment therapy are receiving increasing attention with regard to promoting illness acceptance [44]. A study

of people with hypertension shows that illness acceptance is an important factor contributing to a higher level of adherence to nonpharmacological therapy (e.g. healthy eating habits), preventive behaviors, and positive mental attitude, but has no influence on adherence to pharmacological treatment [39].

Further research is needed to investigate the role of illness acceptance in adherence and other health-related outcomes, and how to improve illness acceptance.

Illness cognition

Adherence is influenced in particular by patient beliefs and misconceptions about medication [15]. Beliefs about medicines are associated with medicine-use patterns among the general population [45] and in chronic disease, such as in asthmatics [46]. Patients beliefs about inhaled corticosteroids correlate with self-reported adherence, as well as an objective adherence measure, calculated by pharmacy dispensing records [47].

A survey study of patients with Crohn's disease showed that beliefs about medicine at initiation of treatment were positively related to adherence. Furthermore, beliefs about medicine have a mediating role in the relationship between satisfaction and adherence [48].

A randomized controlled experiment investigated the causal relationship between treatment beliefs and the placebo effect with a pain reduction cream in a cold pressure task [49▪]. As a clinical conclusion from these findings the variation in placebo analgesia could be predicted by pretreatment necessity beliefs.

Another important aspect is shared decision making. An experimental study showed that not giving patients a choice of medication increased the nocebo effect and reduced the placebo response to the treatment [50].

Fear of side-effects

Many patients are nonadherent because of concerns about side-effects. In addition, the majority of side-effects are nonspecific symptoms that may not be attributed to the pharmacodynamics of the medication [51]. Nonspecific side-effects are associated with individual patient factors such as fear, distress, reduced quality of life [52], and nonadherence [53]. Important concepts in this context are the beliefs and expectations of a patient about unwanted treatment effects [54].

Many studies confirm elevated but similar patterns of side-effects in verum versus placebo groups, and, correspondingly, many patients in placebo groups discontinue the treatment because of side-effects [55]. In addition, 71% of patients with cancer reported at least two symptoms after taking a placebo [56] and every third person who discontinued the antidepressant treatment because of medication-induced side-effects was in the placebo group [57].

In clinical practice, it can be essential to discuss patient's beliefs, their potential ambivalence to treatment, and the heterogeneous origin of adverse events with the patient. The interpretation of occurring side-effects as a sign of effectiveness, and information that side-effects are unpleasant but not a physical threat, can be helpful [5].

A recent clinical trial in patients with breast cancer evaluated the role of patients' pretreatment expectations in the long-term treatment outcome of adjuvant endocrine treatment [58▪]. Adherence rates for this very effective oral anticancer treatment have frequently been reported to be alarmingly low [59]. Specifically, the high side-effect load is discussed as being associated with patients prematurely discontinuing treatment. Results of this prospective cohort study showed that patients with negative initial treatment expectations experienced almost twice as many side-effects after two years of antihormonal treatment as patients with initially neutral expectations. In addition to more intense treatment-emergent side-effects, patients with negative expectations also reported a lower health-related quality of life and higher rates of nonadherence over the 2-year course of the study [58▪]. To conclude, patients' expectations constitute a potentially modifiable factor in relation to side-effects and adherence. Psychological interventions to manage patients' expectations at the outset of a medical treatment might be a beneficial means to prevent nocebo-related treatment side-effects and optimize adherence [60,61]. In an experimental design, it was shown that a psychoeducational intervention, which involves improved medical education about the efficacy and side-effects, increased the adherence [19▪].

Cognitive impairment

Medication nonadherence is a special problem in older adults with cognitive impairment [62]. Potential barriers to adherence are forgetfulness, lack of understanding [63], implementation of medication administration into daily routine, physical problems [64], medical comorbidity and polypharmacy [65], living alone, and the high costs of care [62].

A systematic review by Smith *et al.* [66] showed that deficits in cognitive function involving learning, memory, and executive functions (e.g. in persons with dementia or cognitive impairment) are

risk factors for nonadherence. In a cross-sectional study by Campbell *et al.* [67], 83% of all participants with a mild cognitive impairment reported at least one and 62.5% two or more barriers to medication adherence. The most frequently reported barriers were difficulty remembering the amount and time of each medication intake (49%), difficulty opening or reading prescription bottles (42%), feeling worse when taking medications (29%), and trouble affording medication (26%).

There are different kinds of intervention to improve adherence. Some interventions emphasize self-management components like information, communication, skills training, and social support. Some components of the self-management concepts can be effectively conceptualized as group-based interventions [68]. In a review of studies investigating older persons with cognitive impairment or dementia [69], interventions to improve adherence included alternative dosage forms [70], applying medication once instead of twice a day [71], multicompartment pillboxes [72], medication reminder aids (e.g. placing medicines in a routinely used area) [73], and reminder devises such as an automatic pill dispenser [74].

Telecommunication technology [75] and medication reminder devices [74] were used to assess medication self-administration in participants with dementia, and revealed promising results in these populations.

Further research is needed to replicate these findings. It is still important to develop tailored interventions for this population. A further meta-analysis of interventions to enhance medication adherence in older adults with multiple prescriptions was recently announced by Cross *et al.* [76]. Finally, in patients with developing dementia and other cognitive problems, the involvement of significant others and further social network partners is an option to be considered.

Relationship between patient and healthcare provider

A good relationship between the patient and the healthcare provider is related to higher reported quality of life, higher treatment satisfaction, and a better prognosis [77]. The physician's communication skills, as a central component, are significantly associated with adherence [78].

There are different pathways to improve the relationship of the patient with the healthcare provider [19▪]. It is important to enhance the patient's involvement and encourage active doctor–patient cooperation. A patient-centered approach is recommended, considering spiritual and psychological dimensions, which may be important for the patient, and an accurate recognition of possible problems in the communication.

A meta-analysis by Kelley *et al.* [79] showed the positive effect of the relationship between the patient and the provider on health-related variables. Eight of the 13 studied interventions were assessed to improve communication skills. Three studies used motivational interviewing, each one focusing on shared decision-making, patient-centered care, empathic care, and culture competency training. Both objective data (e.g. hypertension) and validated patient reported (e.g. pain assessment) were evaluated. Overall, the 13 studies showed a small but statistically significant ($P = 0.02$) effect size ($d = 0.11$; range $d = -0.23$ to 0.66) of healthcare outcomes and the patient–clinician relationship. This is consistent with a meta-analysis by Zolnierek and DiMatteo [78], where communication trainings for physicians enhanced patients' adherence.

In addition, the availability of the healthcare provider has an influence on the adherence of patients with chronic diseases [80,81]. This includes regular consultations, being available for questions or emergencies, as well as short waiting times during consultations or even between consultations.

Comorbid depression

Persons who are diagnosed with a chronic disease have a higher risk of developing symptoms of depression [82]. A meta-analysis by Sin and DiMatteo [83] showed a significant association between depression and nonadherence in patients with HIV. That effect is valid in different patient populations [84▪,85] and results in negative health outcome including reduced quality of life [82].

A recent meta-analysis by Sin and DiMatteo [83] showed that the treatment of depression and psychological stress improves medication adherence in antiretroviral therapy. The adherence of a person was 83% higher if he/she received treatment for comorbid depressive symptoms. Interventions were more effective if they were specially targeting depression and of longer duration. In addition, a study on adjuvant hormonal therapy of breast cancer survivors demonstrated that depression mediated the relationship between physical and cognitive symptoms, social support, and adherence to medication [86].

The efficacy of psychological and pharmacological interventions in RCTs to reduce depressive symptoms was also shown in a Cochrane review among persons with diabetes [87]. In eight studies, depression could be reduced by psychological interventions (range of standardized mean differences = 1.47–0.14). The

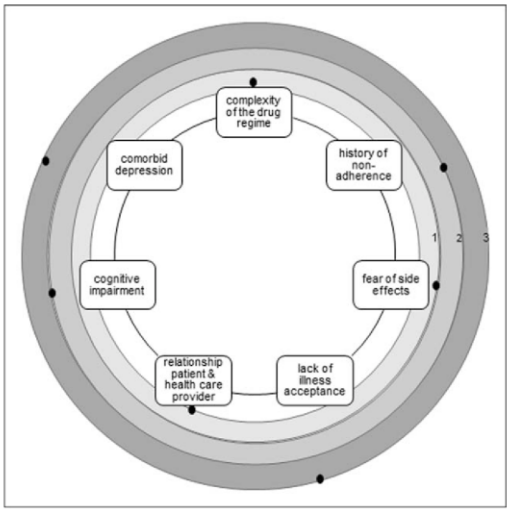

FIGURE 2. Risk profile for nonadherence (an example).

majority of the interventions were used in a face-to face setting, but web-based interventions seemed to be an expedient addition. A meta-analysis by Richards and Richardson [88] showed evidence of web-based interventions in different populations for the reduction of depressive symptoms ($d = 0.56$). One problematic aspect of Internet-based interventions is the relatively high attrition rate [89]. Therefore the use of features such as videos, audio, interactive elements, and mobile support might be helpful.

Up to now, only a few RCTs focus on treating comorbid depression in chronic disease, although comorbid depression has been shown to predict nonadherence. Therefore, further research should focus on populations with a high risk of developing depressive symptoms.

CONCLUSION

The aim of this narrative review was to provide an overview of a selection of frequently neglected risk factors for nonadherence and corresponding interventions to improve adherence. This should give an update and stimulate further research. Even after four decades of identifying the problem, nonadherence remains a challenge for research and for healthcare professionals.

To tackle the nonadherence problem in the population with chronic diseases, we recommend estimating a patient's individual risk of nonadherence and defining a risk profile (Fig. 2) prior to treatment onset. In this risk profile, all factors mentioned above which might promote nonadherence should be considered. The factors could be rated as 1 (low), 2 (medium), or 3 (high) risk of nonadherence. This individual risk profile could be a useful tool for clinical practice. Individual interventions should be tailored according to the particularities of the individual risk profile [4▪].

The above-mentioned risk factors have all shown an influence on adherence in empirical studies. Despite some research focusing on the risk factor 'complexity of the drug regimen' and on the relationship of the patient with the healthcare provider, interventions revealed only moderate or mixed results in enhancing adherence. Other risk factors, such as the history of nonadherence, fear of side-effects, lack of cognitive impairment, comorbid depression, and cognitive impairment have been discussed in the literature but not targeted in intervention studies. Although neglected in studies, they offer potential for improving adherence programs.

For clinical practice, it is important to elaborate and discuss the subjective disease model of the patient. Strategies to enhance adherence should consider the aspects of illness acceptance, treatment necessity beliefs, fear of possible side-effects, and beliefs about the specific medicine or treatment. The treatment of comorbid depressive symptoms should be integrated with the treatment of chronic diseases, and the risk of cognitive decline should be taken into consideration when anticipating adherence problems, especially in older patient populations. Only prior psychological definition of nonadherence risks offers the opportunity to intervene before nonadherence is established as a behavioral pattern.

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Conflicts of interest

There are no conflicts of interest.

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A. 2 Studie 2

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Studie 2 (Manuskript): Validierung AdRisk

Will this Patient become Non-Adherent?

Predicting Non-Adherence in Chronic Diseases with the Adherence Risk Profile (AdRisk)

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Abstract

Background: Medication non-adherence is a common problem in the treatment of chronic diseases. Previous studies have identified several barriers to medication adherence, but these factors are not systematically used to better predict non-adherence. The present study aims to develop and validate the Adherence Risk Profile (AdRisk), a new screening instrument to predict non-adherence and to identify patients at risk for non-adherence. **Methods:** The web-based sample consisted of 677 patients with chronic conditions. They reported a diagnosis of Crohn's disease, type 2 diabetes mellitus, chronic-obstructive-pulmonary-disease, hypertension, rheumatoid arthritis, or epilepsy, and were treated with medication. Standard item, reliability, and test-retest reliability analyses were computed. To investigate the factorial structure, the sample was divided into two subsamples. A maximum likelihood (ML) factor analysis was conducted for subsample A and a confirmatory factor analysis (CFA) for subsample B. To examine concurrent validity, the instrument's two overall scores (ART, BT) and the four subscales were tested for their associations with adherence (assessed via the MARS-D). **Results:** The AdRisk scores and subscales showed significant relations to adherence, confirmed by hierarchical multiple regressions. The scale displayed good internal consistency (Cronbach's α=.82; n=677) and test-retest reliability after 4 weeks was α=.83 (n=286). Results indicated good convergent validity. The VR factor analysis extracted four components, explaining 61 percent of variance, confirmed by the CFA. **Conclusion:** The AdRisk displayed good psychometric characteristics. It should be used as an economic screening tool to assess a broad range of psychological barriers to medication adherence, and to identify patients at risk for non-adherence.

Keywords: medication adherence, psychological barriers, screening, chronic disease, Adherence Risk Profile (AdRisk)

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Background

Adequate adherence, which can be defined referring to the World Health Organization (WHO) as "the extent to which a person´s behavior-taking medications, following a diet, and/or executing lifestyle changes corresponds with agreed recommendations from a health care provider" (Sabaté, 2003), is essential for realizing the potential health benefits of a medical treatment. Scientific publications have reported average medication non-adherence (NA) rates ranging from 22 percent to 57 percent for patients with various chronic diseases (Osterberg & Blaschke, 2005). This indicates that many patients experience difficulties in adhering to a recommended treatment plan and medication adherence poses, until now, a major challenge in the everyday lives of patients, their provider, and the health care system (Brown & Bussell, 2011).

For the adequate treatment of patients with chronic somatic diseases, it is necessary to develop effective and practical interventions to enhance medication adherence (Hahn et al., 2008). In the last years, there has been substantial research on interventions with the purpose of improving medication-related adherence (Kini & Ho, 2018; Kripalani, Yao, & Haynes, 2007; Nieuwlaat et al., 2014; Viswanathan et al., 2012). However, until now, there is a lack of efficacy of interventions, especially in regard to long-term adherence and health outcomes (Viswanathan et al., 2012). Different aspects have been discussed to explain this lack of efficacy. However, there is the recommendation to differentiate between unintentional and intentional non-adherence (NA) (Horne et al., 2005; Wilke, Müller, & Morisky, 2011). So far, interventions have been unable to customize the individual needs and preferences of patients (Allemann, Nieuwlaat, van den Bemt, Hersberger, & Arnet, 2016). There is evidence that a variety of factors (adherence barriers) can contribute to the development of NA (Osterberg & Blaschke, 2005). However, according to the WHO (Sabaté, 2003), (medication) adherence is a complex and multidimensional construct which is influenced by factors of the health system, socioeconomic and patient-related factors, and therapy-related and disease-specific factors. In accordance with existing literature, adherence barriers can be classified into three main groups.

The most frequently observed *medication-related barriers* were the complexity of the medication regime (Ingersoll & Cohen, 2008) and fear of/experience with side effects (Foot, La Caze, Gujral, & Cottrell, 2016; Holmes, Hughes, & Morrison, 2014; Horne et al., 2013).

In the category *health care system-related barriers*, the (in)direct costs of the medication-related treatment (Maciejewski, Farley, Parker, & Wansink, 2010) and the quality of the physician-patient interaction (cognitive and emotional) were observed (Vangeli et al., 2015).

Factors associated with *patient-related (un)intentional barriers* were general attitudes toward the treatment and medication (Foot et al., 2016; Holmes et al., 2014; Horne et al., 2013)

or health beliefs (e.g., perceived controllability and treatability) (Kucukarslan, 2012; Kurpas, Mroczek, & Bielska, 2013; Kurpas, Mroczek, Knap-Czechowska et al., 2013; Lewko et al., 2007); knowledge about the disease and the treatment (Bourbeau & Bartlett, 2008; Horne, Hankins, & Jenkins, 2001); self-efficacy (Houston & Fominaya, 2015; Rogliani, Ora, Puxeddu, Matera, & Cazzola, 2017; Vangeli et al., 2015); and previous adherence behavior (Glombiewski, Nestoriuc, Rief, Glaesmer, & Braehler, 2012). Other important elements are the presence of symptoms of depression and anxiety (Crawshaw, Auyeung, Norton, & Weinman, 2016; Cully et al., 2006; DiMatteo, Lepper, & Croghan, 2000) and the level of perceived stress (Morisky, Ang, Krousel-Wood, & Ward, 2008; Shallcross et al., 2015).

There is evidence that the present psychological factors influence medication adherence, so far neglected in clinical practice (Arlt, Nestoriuc, & Rief, 2017).

The detection of relevant barriers to medication adherence is a necessary initial step to be able to address individual problems and increase adherence. According to Allemann et al. (2016), medication adherence can only be achieved by integrating the factors that facilitate or obstruct it, whereby the prevalence of every single barrier poses a risk for non-adherence. Thus, patients' individual barriers to medication adherence should be assessed to identify those at risk and to effectively address these risk factors with tailored interventions.

Self-report measures offer a practical and flexible method of assessing adherence. Their results have been linked to several clinical outcomes (Morisky, Green, & Levine, 1986). Until now, various scales have been developed to assess single or a few associated predictors. These tools have mainly been created to be used for specific chronic diseases (Horne, Weinman, & Hankins, 1999; Moss-Morris et al., 2002; Schmitt et al., 2014). However, there are only limited possibilities to assess a broad range of barriers to medication adherence economically. Although some tools already cover various adherence influencing factors, some barriers and facilitating factors that have been shown to be of relevance are missing (Hahn et al., 2008; Müller, Kohlmann, & Wilke, 2015). Furthermore, other tools assessing various barriers are restricted to specific groups of patients; consequently, their application in clinical practice is limited (Kawakami et al., 2014; Moss et al., 2014).

Therefore, the purpose of this study was to develop the Adherence Risk Profile (AdRisk), a screening tool assessing a broad range of psychological barriers to medication adherence while also being applicable to various chronic diseases. This instrument should identify patients at increased risk for non-adherence. The aim was to develop a reliable and valid instrument to identify persons at risk for non-adherence, preferably before non-adherence occurs, to offer options for early interventions.

Studie 2 (Manuskript): Validierung AdRisk

Methods

Development of the AdRisk

A literature search on barriers to medication adherence was conducted. The following aspects served as guidelines for the development of the instrument. Firstly, the selected barriers have repeatedly been shown to be associated with medication adherence. Secondly, the selected risk factors should be relevant to patients with different chronic diseases, and they should be sensitive to change. Finally, the instrument was intended to be short and easy to apply and interpret in different clinical settings, as well as in clinical research.

Test Description: The Adherence Risk Profile (AdRisk)

The AdRisk (see Appendix 1) is a 16-item self-report screening tool assessing twelve barriers to medication adherence and current medication adherence itself. Medication adherence itself is measured via one item asking the patient to rate the frequency with which he/she has taken his/her medications as prescribed by their doctor during the past four weeks on a five-point scale from 0 (never) to 4 (always). Furthermore, patients are asked to rate their agreement with 15 statements describing beliefs, emotional states, and behaviors acting as barriers to medication adherence on a five-point Likert scale (0 = strongly disagree, 1 = disagree, 2 = neither, 3 = agree, 4 = strongly agree). The following twelve barriers and facilitating factors to medication adherence are depicted: controllability (personal control item 2, treatment control item 3), acceptance of disease (item 4), satisfaction with information about medicines (item 5, item 6), self-efficacy for medication management (item 7), necessity of medication (item 8), concern about side effects (item 9), doctor-patient interaction (item 10, item 11), depression (item 12), anxiety (item 13), perceived stress (item 14), general past behavior regarding medication intake (item 15), and general critical beliefs about medicines (item 16). The screening tool leads to an individual profile of barriers to medication adherence, enabling the practitioner to understand specific needs for assistance and to give individualized support to pursue adherent behavior. An additional total score (AdRisk Total, ART) and a score representing the number of barriers present (Barriers Total, BT) can be obtained. The AdRisk Total is assessed by reverse coding of items 2–8, 10, 11, and 15, and subsequently adding up items 2–16. The resulting score ranges between 0 and 60, with higher ART scores representing higher risk for non-adherence. After reversing items 2–8, 10, 11, and 15, the Barriers Total score is built by assessing the number of items with a minimum score of 2 (neither agree nor disagree) or higher. A higher BT score represents a higher number of barriers present.

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Sampling and Procedure

The local ethics committee approved the study. Participants diagnosed with one of six different chronic diseases (Crohn's disease, type 2 diabetes mellitus, chronic obstructive pulmonary disease, hypertension, rheumatoid arthritis, or epilepsy) were eligible to take part in the study.

Recruitment took place via flyers and notices distributed in pharmacies, doctors' offices, and clinics, mailing lists, the websites of patient organizations, support groups for patients on a social media platform, and notice of the study in a local newspaper. As an incentive, the participants had the chance to win one of four €50 vouchers for an online store. Inclusion criteria were defined as follows: adults aged 18 years or older, self-reported diagnosis of at least one of the six chronic diseases, and treatment including medication intake.

The survey was carried out online via the website unipark.com (QuestBack GmbH). On the first page of the survey, the participants were informed that their answers would be anonymous and, by clicking a button, they provided informed consent. Furthermore, the participants could discontinue the survey at any time by leaving the website.

The study consisted of two parts. During the first part, participants were asked to give demographic information (age, gender, marital status, nationality, mother tongue, highest educational qualification, occupational status, and monthly net household income), as well as disease and therapy-related information (chronic disease and time living with the disease, number of medications, number of further diseases, and medications). Subsequently, participants answered the AdRisk and filled in further questionnaires used in the order specified in the Measures section below.

To ensure anonymity, at the end of the questionnaire the participants received a link to a second, unrelated web-based survey to provide their e-mail address. Four weeks later, participants received an invitation to the second survey. After completing the second survey, the participants could register for the lottery (unrelated web-based survey, same procedure as described beforehand).

Measures

Medication adherence. To assess medication adherence, the German version of the Medication Adherence Report Scale (MARS-D; Mahler et al., 2010) was used. The MARS-D comprises five items describing non-adherent behavior (e.g., "Some people forget to take their medicines. How often does this happen to you?"). Participants were asked to rate the frequency of those behaviors on a five-point scale from 1 (always) to 5 (never), leading to a sum score, higher scores representing higher medication adherence. In the scope of the initial validation of

the German version, Mahler and colleagues (2010) found a moderate to acceptable internal consistency with Cronbach's α ranging between .60 and .69. The internal consistency found in this study can be considered acceptable (α = .76).

Acceptance of illness. The Acceptance of Illness Scale (AIS; Felton & Revenson, 1984) was translated from English into German by two experienced researchers in the field fluent in both languages. Using both translations, a final version was administered. The scale consists of eight items (e.g., "I have problems with adapting to limitations imposed by my illness"), which have to be rated on a five-point scale from 1 (strongly agree) to 5 (strongly disagree). A score is obtained by totaling the items, a higher score representing higher acceptance of illness. The German version showed good internal consistency (α = .80), comparable to the English version (α = .82; Felton & Revenson, 1984).

Satisfaction with information about medicines. To measure satisfaction with information about medicines, the German version of the Satisfaction with Information about Medicines Scale (SIMS-D; Mahler et al., 2009) was used. Participants were asked to rate the information received about several aspects of their medicines (e.g., "What your medicine is for") on a five point scale: too much, about right, too little, none received, and none needed. For the work at hand, only subscale 1 (items 1–9) assessing satisfaction with information about action and usage of medication is of relevance. Higher subscale scores indicate higher satisfaction. In previous research, internal consistency for subscale 1 was shown to be good (α = .87; Mahler et al., 2009). For the present sample, internal consistency was good, too (α = .85).

Quality of physician-patient interaction. The German version of the Questionnaire on the Quality of Physician-Patient Interaction (*Engl.* QQPPI, *German* FAPI; Bieber, Nicolai, Mueller, & Eich, 2011) was used to assess the quality of physician-patient interaction. The FAPI is composed of 14 items (e.g., "The physician seemed to be genuinely interested in my problems"). Participants were asked to rate these statements on a five-point scale ranging from 1 (I do not agree) to 5 (I fully agree), higher mean scores representing better quality physician-patient interaction. In previous research, the scale showed excellent internal consistency (α = .97) and its one dimensional structure was replicated for the German version (Bieber et al., 2011). Internal consistency in this sample can also be considered excellent (α = .97).

Personal control and treatment control. To assess personal control and treatment control, the corresponding scales of the German version of the Illness Perception Questionnaire-Revised (IPQ-R; Glattacker, Bengel, & Jäckel, 2009) were used. The two subscales each consist of four items IPQ-R scales measuring personal control (e.g., "There is a lot which I can do to control my symptoms") and treatment control (e.g., "The negative effects of my illness can be prevented (avoided) by my treatment"). Participants had to rate their approval of the statements on a five-point scale ranging from 1 (strongly disagree) to 5 (strongly agree). Higher mean scores

represented the experience of higher personal control and higher treatment control respectively. In a first psychometric evaluation of the German version, the scales had good internal consistencies (α = .80 each). Internal consistencies in this study were good for the subscale personal control (α = .85), but low for the subscale treatment control (α = .61).

Self-efficacy for appropriate medication use. The Self-Efficacy for Appropriate Medication Use Scale (SEAMS; Risser, Jacobson, & Kripalani, 2007) was applied to measure self-efficacy for medication use. The scale was translated into German using the same procedure described previously. Participants were asked to rate their confidence in taking prescribed medications correctly in various situations (e.g., "How confident are you that you can take your medicines correctly if your normal routine gets messed up?"). Thirteen items had to be rated on a three-point scale ranging from 1 (not confident) to 3 (very confident), resulting in a sum score with higher values indicating higher self-efficacy for medication use. Our German version showed an excellent internal consistency (α = .91), which was comparable to the English version (α = .89; Risser et al., 2007).

Beliefs about medicines. To measure beliefs about medicines, the German version of the Beliefs about Medicines Questionnaire (BMQ; Mahler et al., 2012) was used. The questionnaire comprises 18 items belonging to four subscales. Participants were asked about their beliefs concerning the need for their medicines in terms of maintaining their health (specific necessity subscale, five items), concerns regarding medication intake (specific concerns subscale, five items), and more general beliefs about medicines regarding potential harm (general harm subscale, four items) and overuse (general overuse subscale, four items). Each item had to be rated on a five-point scale from 1 (strongly disagree) to 5 (strongly agree). Higher subscale sum scores indicated a higher belief in the personal need for medicines to maintain health, stronger concerns about medications, and a more negative point of view on medicines in general and how they are prescribed. Example items are "My medicines protect me from becoming worse" (specific necessity subscale); "I sometimes worry about the long-term effects of my medicines" (specific concerns subscale); "Medicines do more harm than good" (general harm subscale), and "Doctors use too many medicines" (general overuse subscale). In the scope of previous research, the subscales showed acceptable to good internal consistencies (α = .79–.83; Mahler et al., 2012). Internal consistencies found in this study can be considered good (α = .79–.89).

Previous medication adherence. The Rief Adherence Index (RAI; (Glombiewski et al., 2012) was used to assess adherence as a behavior pattern independent of current medication intake. The scale consists of four items describing adherence-related behaviors (e.g., "I discontinued my medication earlier then recommended by the doctor"), which had to be rated on a five-point scale ranging from 1 ([almost] never happened [in 0–20% of cases]) to 5

([almost] always happened [in 80–100% of cases]). In order to obtain a general behavior pattern, participants were instructed to take into account "all past behaviors concerning any prescribed medication'' (Glombiewski et al., 2012). Higher RAI sum scores reflect higher general non-adherence in the past. The scale showed satisfactory internal consistency (α = .79) (Glombiewski et al., 2012). Internal consistency in this sample was acceptable (α = .74).

Stress. The level of perceived stress was assessed using the German version of the Perceived Stress Scale (PSS-10; Klein et al., 2016). The PSS-10 consists of ten items (e.g., "In the last month, how often have you felt nervous and stressed?") which have to be rated on a five-point scale from 0 (never) to 4 (very often). Higher levels of perceived stress are represented by higher sum scores. In previous research, internal consistency for the overall scale was good (α = .84; Klein et al., 2016). Internal consistency in this study was also good (α = .90).

Depression. To assess depression severity, the German version of the Patient Health Questionnaire (PHQ-9; Löwe et al., 2004) was used. The PHQ-9 comprises nine items asking for the frequency with which participants had been bothered with symptoms of depression during the past two weeks (e.g., "feeling down, depressed, or hopeless") on a four-point scale from 0 (not at all) to 3 (nearly every day). Summing up those nine items leads to a total score with higher values indicating higher depression severity. A tenth item asks for the patients` overall rating of symptom-related impairment. The German version of the scale in a prior study showed good internal consistency (α = .88; Löwe et al., 2004). Equally good internal consistency was found in this study (α = .88).

Anxiety. The German version of the seven-item Generalized Anxiety Disorder Scale (GAD-7; Löwe et al., 2008) was used to assess anxiety severity. Core symptoms of generalized anxiety disorder are described (e.g., "Feeling nervous, anxious, or on edge"), and participants were asked to indicate how often during the past two weeks they had been bothered by each of the symptoms on a four-point scale ranging from 0 (not at all) to 3 (nearly every day). The resulting sum score is used as an indicator for anxiety symptom levels, higher scores representing higher levels of anxiety. The German version of the scale showed good internal consistency (α = .89). Internal consistency found in this study was also good (α = .90).

Appendix 2 presents a table summarizing the factors influencing medication adherence that are assessed by the AdRisk items. The table also includes the validation scale and its reported internal consistency.

Participants

Sample. In total, 952 participants provided their informed consent. Of the remaining participants, 129 failed to meet the inclusion criteria: 101 did not suffer from any chronic disease of relevance for the study, five were younger than 18, and 23 did not receive medication

as a treatment. Thus, 823 participants fulfilling the inclusion criteria remained. Of these, 132 ceased answering before they had completed all the questionnaires and were excluded from further analyses. Therefore 691 participants finished the questionnaire, of whom a further 14 participants were excluded because of implausible data (8), dual participation (4), and systematic answer patterns (2).

The final sample forming the basis of our analyses consisted of 677 participants with a mean age of 46.04 years; 77.3 percent were female. Participants were diagnosed with diabetes (n=60), hypertension (n=87), COPD (n=140), rheumatoid arthritis (n=149), epilepsy (n=70), or Crohn's disease (n=171). On average, they had been diagnosed 10.6 years previously and took 2.6 different medications as a treatment for their disease. Furthermore, 64.8 percent of the participants stated that they had been diagnosed with another disease. For more details, see Table 1. For further information on the sample's characteristics, see Appendix 3.

In total, 565 participants were registered for the second survey. Of those, 468 provided informed consent for part two, of whom 14 participants were excluded because of double cases. In sum, 290 participants could be assigned to survey parts one and two by their individual code, while four were excluded because of missing data.

Table 1. Sample Characteristics

Variable	n (%)
Demographics	
Age	
Mean ± SD	46.04 ± 14.6
Range	18–80
Gender	
Male	154 (22.7)
Female	523 (77.3)
Mother tongue	
German	665 (98.2)
Other	12 (1.8)
Monthly net household income	
<750 euros per month	78 (11.5)
750–1249 euros per month	141 (20.8)
1250–1999 euros per month	192 (28.4)
≥2000 euros per month	266 (39.3)
Disease-related information	
Chronic disease for the study	
Diabetes mellitus type 2	60 (8.9)
Hypertension	87 (12.9)
Chronic obstructive pulmonary disease	140 (20.7)
Rheumatoid arthritis	149 (22.0)
Epilepsy	70 (10.3)
Crohn´s disease	171 (25.3)
Time since diagnosis (in years)	
Mean ± SD	10.6 ± 10.3
Range	0.1–62.0
Number of medications prescribed for the treatment of the for the study relevant disease	
Mean ± SD	2.6 ± 1.7
Range	1–11

Notes. [a] Other languages indicated were Bosnian (1), Greek (2), English (1), Italian (1), Dutch (1), Polish (2), Slovenian (1), Turkish (2), and Ukrainian (1). n=677.

Data Analysis

SPSS Statistics and SPSS AMOS (version 25, IBM) were used to compute item difficulty, item total correlations (with the item itself excluded from the scale), Cronbach's α for items 2–16 representing the AdRisk's overall scale, internal consistency (Cronbach's α), and test-retest reliability. The retest interval was four to six weeks (M = 4.3; SD = 0.7; range 4–6). To examine convergent validity, Spearman correlations were used to test for associations between the items and established scales measuring the same construct. To investigate the factorial structure, exploratory (EFAs) and confirmatory factor analyses (CFAs) were used. For this purpose, the sample was randomly divided into two subsamples (A and B). Independent t-tests were used to analyze differences between the two subsamples regarding age, number of medications,

complexity of the medication intake, disease duration (years), MARS-D score, and ART, while binary variables were analyzed using a χ^2 test. The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity were calculated. A varimax rotated (VR) factor analysis was conducted for subsample A. An eigenvalue of 1 was the criterion to determine the number of components to be extracted. For subsample B, a CFA was computed to test the fit of the component structure that resulted from the VR analysis. As goodness of fit measures, the χ^2 test, root mean square error of approximation (RMSEA), standardized root mean squared residual (SRMR), and comparative fit (CFI) are reported. In order to examine the instruments' concurrent validity, the two overall scores (ART, BT) and the four subscales were tested for their associations with adherence. Six hierarchical multiple regression analyses were conducted. In a first step, patient-related factors (age, gender, and income) were entered into the regression analyses; in a second step, the treatment-related factor (number of medications) and in a third step the respective total score for subscales of the AdRisk were entered. R^2, adjusted R^2, and increase in R^2 (ΔR^2) are provided. The association between adherence (MARS-D Score) and single items (1-16) was calculated using Spearman correlations (95% bootstrap; one-tailed). Little's (1988) MCAR test revealed that missing values were missing completely at random (MCAR); χ^2 (1968, n=677) = 1872.090, p = .939. As MCAR was given and the percentage of missing values for the final data set was very low (0.02%), missing values were excluded using pairwise deletion.

Studie 2 (Manuskript): Validierung AdRisk

Results

Item statistics. Appendix 1 displays the AdRisk items (German and English version) and gives an overview of the item responses. Item difficulties varied from *Pi* = 14.00 (item 7) to *Pi* = 62.75 (item 14), with a mean difficulty of *Pi* = 33.53. The item-total correlation of the individual items with the total score ranged from *r*itc = .27 (item 16) to *r*itc = .64 (item 5), with a mean item-total correlation of *r* = .44. The internal consistency of the whole scale was α = 82 and the consistency would not have benefitted from removing any item (see Table 2). The test-retest reliability was α = .83 (n=286).

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Table 2. Item and scale characteristics of the AdRisk

Item/ Score	Assessed influencing factor	*M*	*SD*	Item difficulty	Item-total correlation	Cronbach's α if item removed
1	Current medication adherence	3.72	0.67	93.00	/	/
2[a]	Perceived controllability	1.10	0.99	27.50	.30	.82
3[a]	Perceived treatability	0.81	0.75	20.25	.40	.81
4[a]	Illness acceptance	1.09	1.07	27.25	.41	.81
5[a]	Satisfaction with information about medicines	0.80	0.97	20.00	.64	.79
6[a]	Satisfaction with information about medicines	0.65	0.83	16.25	.57	.80
7[a]	Self-efficacy for appropriate medication use	0.56	0.72	14.00	.45	.81
8[a]	Attitude toward own medication	0.88	0.91	22.00	.30	.82
9	Concerns about side effects	2.46	1.24	61.50	.35	.81
10[a]	Physician-patient interaction (cognitive)	1.29	1.13	32.25	.62	.79
11[a]	Physician-patient interaction (emotional)	1.26	1.15	31.50	.54	.80
12	Depression	2.06	1.30	51.50	.51	.80
13	Anxiety	1.63	1.27	40.75	.49	.80
14	Level of perceived stress	2.51	1.20	62.75	.42	.81
15[a]	Past adherence behavior	0.77	0.82	19.25	.32	.81
16	Attitude toward medication in general	2.25	1.19	56.25	.27	.82
ART		20.11	8.38	/	/	/
BT		5.04	2.79	/	/	/

Notes. Item difficulty corresponds to P_i. Cronbach's α corresponds to Cronbach's α if item deleted from the scale. Item 1 assesses medication adherence itself; items 2–16 cover barriers to medication adherence and enter into the total scores. ART = AdRisk Total, sum score for items 2–16; BT = Barriers Total, total score for number of barriers fulfilled. [a]Items were reverse coded for item and reliability analysis. Sample n=677.

Convergent validity. Items 1–6, 8–14, and 16 showed moderate to high correlations with the established scale measuring the same construct (.306 ≤ r ≤ .735, all *ps* < .001). Item 15 showed the expected at least moderate negative correlation (r = -.341, *p* < 001) and item 7 a small correlation with the corresponding subscale (r = .267, *p* < 001) (see Table 3).

Table 3. Correlations between established scales and the corresponding AdRisk items measuring the same construct

Item	Scale	*r*	95% CI
1	MARS-D	.483*	[.419–.535]
2	IPQ-R personal control subscale	.569*	[.512–.623]
3	IPQ-R treatment control subscale	.369*	[.301–.442]
4	AIS	.306*	[.241–.375]
5	SIMS-D subscale 1	.422*	[.358–.490]
6	SIMS-D subscale 1	.328*	[.256–.397]
7	SEAMS	.267*	[.199–.333]
8	BMQ specific necessity subscale	.506*	[.445–.566]
9	BMQ specific concerns subscale	.580*	[.518–.634]
10	FAPI	.686*	[.639–.728]
11	FAPI	.735*	[.692–.774]
12	PHQ-9	.683*	[.638–.723]
13	GAD-7	.608*	[.556–.655]
14	PSS-10	.625*	[.572–.674]
15	RAI	-.341*	[-.409– -.276]
16	BMQ general harm subscale	.411*	[.342–.475]
16	BMQ general overuse subscale	.449*	[.384–.509]

Notes. Spearman correlation coefficients (*r*) are displayed. Unless otherwise noted, scales' total scores were used in calculating correlations. Bootstrap confidence intervals are indicated. Method: percentile, 1,000 samples. MARS-D = German version of the Medication Adherence

Report Scale; IPQ-R = Illness Perception Questionnaire-Revised; AIS = Acceptance of Illness Scale; SIMS-D = German version of the Satisfaction with Information about Medicines Scale; SEAMS = Self-Efficacy for Appropriate Medication Use Scale; BMQ = Beliefs about Medicines Questionnaire; FAPI = *Engl*. QQPPI, Questionnaire on the Quality of Physician-Patient Interaction; PHQ-9 = nine-item Patient Health Questionnaire; GAD-7 = seven-item Generalized Anxiety Disorder Scale; PSS-10 = ten-item Perceived Stress Scale; RAI = Rief Adherence Index; CI = confidence interval; * $p < .001$, two-tailed; n=677.

Factor structure. The two subsamples A and B did not differ regarding age, gender, number of medications, complexity of the medication regime, type or duration of the chronic disease, MARS-D score, and AdRisk score (Table 4).

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Table 4. Characteristics of the two subsamples resulting from the random division of the total sample for the purpose of exploratory and confirmatory factor analyses

	Subsample A (n=342)		*Subsample B (n=335)*				
	M	SD	M	SD	t	*df*	*p*
Age (years)	45.9	14.9	46.2	14.4	-.340	675	.734 (n.s.)
Number of medications[a]	2.6	1.6	2.6	1.8	.216	675	.829 (n.s.)
Complexity index[b]	5.7	2.5	5.5	2.7	.947	675	.344 (n.s.)
Disease duration[a] (years)	10.0	9.9	11.3	10.6	-1.654	658	.099 (n.s.)
MARS-D score	22.7	2.5	22.7	2.8	.018	675	.986 (n.s.)
AdRisk score	20.2	8.5	20.0	8.2	.427	675	.669 (n.s.)

					χ^2	*df*	*p*
Chronic disease[a] (*n* for sample A and B)	Dm2	35	25				
	Hypertension	43	44				
	COPD	68	72				
	RA	82	67				
	Epilepsy	37	33				
	CD	77	94		5.149	5	.398 (n.s.)

	Women	*Men*	*Women*	*Men*	χ^2	*df*	*p*
Gender	270	72	253	82	1.130	1	.166 (n.s.)

Notes. [a] (In relation to the) primary diagnosis for the study; [b] Frequency of daily medication intake x frequency over the week (less than once, once, several times a day). Dm2 = Diabetes mellitus type 2; COPD = chronic obstructive pulmonary disease; RA = rheumatoid arthritis; CD = Crohn´s disease. MARS-D = Medication Adherence Report Scale (German version); n.s. = not significant (p>0.05).

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EFA. For subsample A, Bartlett's test of sphericity (χ^2 = 1859.89, df = 105, p < 0.001) indicated that correlations between the items were sufficiently large for an ML. The KMO criterion was 0.80, demonstrating good suitability of the data for the analysis. On the basis of a varimax rotation, four factors were extracted based on eigenvalues, which explained 61 percent of the variance. Factor 1—'information about medication and physician-patient relationship' subscale—contains items 5, 6, 7, 10, 11, and 15 and explained 21.87 percent of the variance (factor loadings between .611 and .782). Factor 2—'affectivity and acceptance' subscale—involves items 4, 12, 13, and 14 and explained 17.48 percent of the variance (factor loadings between .534 and .878). Factor 3—'controllability of the disease' subscale—consists of items 2, 3, and 8 and explained 11.57 percent of the variance (factor loadings between .707-.804). Factor 4—'fear of side effects and critical attitude toward medication' subscale—contains items 9 and 16 and explained 10.08 percent of the variance (factor loadings .700 and .800) (Table 5).

Table 5. Sample A: VR factor loadings, eigenvalues, and explained variance for the extracted factors for the AdRisk

Item	Influencing factor assessed	Factor 1	Factor 2	Factor 3	Factor 4
5	Satisfaction with information about medicines	.704			.335
6	Satisfaction with information about medicines	.723			
7	Self-efficacy for appropriate medication use	.745			
10	Physician-patient interaction (cognitive)	.782			
11	Physician-patient interaction (emotional)	.760			
15	Past adherence behavior	.611			
4	Illness acceptance		.534		
12	Depression		.878		
13	Anxiety		.813		
14	Level of perceived stress		.806		
2	Perceived controllability			.707	
3	Perceived treatability			.804	
8	Attitude toward own medication			.669	
9	Concerns about side effects				.700
16	Attitude toward medication in general				.800
Eigenvalue		3.280	2.622	1.736	1.512
Explained variance		21.868	17.478	11.572	10.080

Note. Factor loadings <.30 not shown.

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CFA. In order to test the four-factor structure, a confirmatory analysis was calculated on the basis of subsample B (see Figure 1 for the path diagram using standardized path coefficients). The χ^2 was significant: χ^2 (84) = 360.834, p < 0.001, and the χ^2/df ratio was 4.296. The CFI was 0.833, the RMSEA was 0.099 (0.089–0.110), and the SRMR was 0.066.

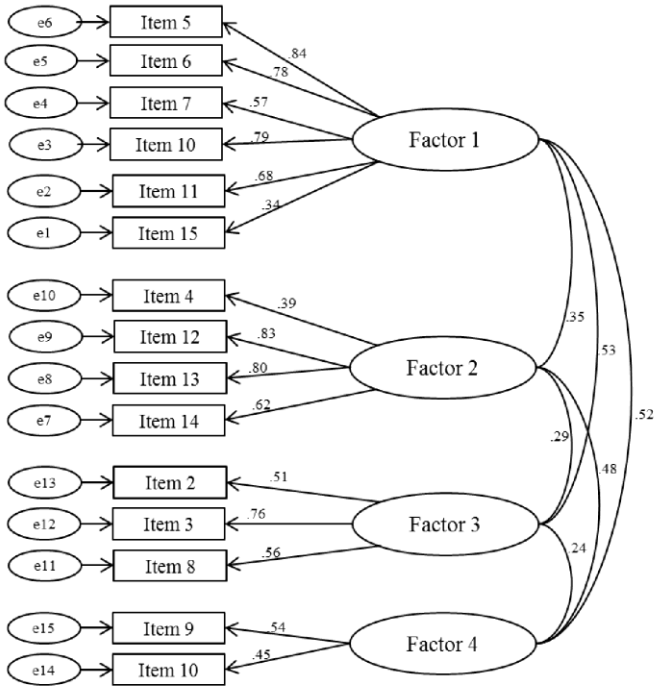

Figure 1. Path diagram for the confirmatory factor analysis with the standardized path coefficients for subsample B (n=335)

Concurrent validity. Table 6 shows the results of the hierarchical multiple regression analyses to evaluate the performance of the two overall scores and the performance of the two overall scores and the four subscales in predicting adherence. The ART, the BT, and the four subscales showed a significant association with adherence over and above age, gender, income, and the number of medications.

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Table 6. Results of the hierarchical multiple regression analyses examining the associations between the AdRisk's items, overall barriers to medication adherence, number of barriers present, and the four subscales with adherence controlled for age, gender, income, and number of medications

	Adherence (MARS)					
Predictor[a]	*B* [LL, UL][b]	*SE B*[c]	β	ΔR^2	R^2	Adjusted R^2
Overall barriers to medication adherence (ART)	-.097* [-.124, -.070]	.014	-.305	.091	.122	.113
Number of barriers present (BT)	-.277* [-.355, -.196]	.041	-.289	.082	.113	.104
Subscale 1: Information about medication and physician-patient relationship (Items 5, 6, 7, 10, 11, 15)	-.231* [-.283, -.183]	.026	-.366	.132	.405	.155
Subscale 2: Affectivity and acceptance (Items 4, 12, 13, 14)	-.056* [-.111, -.003]	.028	-.079	.006	.037	.027
Subscale 3: Controllability of the disease (Items 2, 3, 8)	-.261* [-.401, -.122]	.070	-.195	.037	.069	.059
Subscale 4: Fear of side effects and critical attitude toward medication (Items 9, 16)	-.212* [-.328, -.105]	.057	-.155	.023	.055	.045

Notes. Results of the three steps of six individual hierarchical multiple regression analyses are displayed (first step: age, gender, and income; second step: number of medications; third step: the scores or the subscales). Adherence was assessed using the German version of the Medication Adherence Report Scale (MARS-D). Bootstrapped confidence intervals and standard errors for the regression coefficients are reported. Method: percentile, 1,000 samples. *B* = unstandardized regression coefficient. β = standardized regression coefficient. ΔR^2 = increase in R-squared. ART = AdRisk Total, higher total scores representing higher barriers to medication adherence. BT = Barriers Total, representing the numbers of barriers to medication adherence present. * < .05, two-tailed; n=677.

[a] Predictors included in the third step for the individual hierarchical multiple regression analyses.

[b] 95% bootstrapped confidence intervals [LL = lower level, UL = upper level].

[c] Bootstrapped standard errors for unstandardized regression coefficients.

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The associations between adherence (MARS-D Score) and single items are presented in Appendix 4. Items 1, 7, and 15 showed moderate to high correlations with the MARS-D as an indicator of adherence (-.336 ≤ r ≤ -.487; all ps). Item 2–6, 8–11, and 14–15 showed a small correlation with the adherence scale (-.069 ≤ r ≤ -.225; all ps). Items 12, 13, and 16 did not show any significant correlations (-.026 ≤ r ≤ -.047; all ps).

Discussion

The aim of the study was to validate the recently developed Adherence Risk Profile (AdRisk) on a sample of patients with six different chronic diseases (Crohn's disease, type 2 diabetes mellitus, chronic obstructive pulmonary disease, hypertension, rheumatoid arthritis, and epilepsy). The AdRisk is a self-report screening tool, which is envisioned to assess patients' individual risk for future medication non-adherence by measuring twelve barriers to medication adherence detected by previous research.

Item statistics. The corrected item-total correlations of the items (2–16) were above the threshold of 30.00 (Fisseni, 1997) and indicated a moderate discriminatory power.

Convergent validity. The AdRisk items showed moderate to large associations with the established scales measuring the same constructs. Only item 7 (SEAMS, the Self-Efficacy for Appropriate Medication Use Scale) showed a modest correlation with the corresponding subscale of $r = .30$. This could be explained by differences in the patient populations: until now, mainly disorder-specific questionnaires have been used (Frei, Svarin, Steurer-Stey, & Puhan, 2009).

Factor structure. For the EFA, the ML extracted four factors which explained 61 percent of the variance. The factors are in four subscales: 1. information about medication and physician-patient relationship; 2. affectivity and acceptance; 3. controllability of the disease; and 4. fear of side effects and critical attitude toward medication. The CFA, using a second independent sample, also confirmed the extraction of four factors. The fit indices were all satisfactory, except for the AdRisk, which was slightly below the threshold for an acceptable model fit (Schreiber, Nora, Stage, Barlow, & King, 2006).

Concurrent validity. The two overall scores and the four subscales showed significant associations with adherence over and above patient-related and treatment-related factors. The models accounted for 3.7–40.5 percent of variance of adherence. Contrary to our assumptions, items 12, 13, and 16 did not show significant correlations with the MARS-D. This is in contrast with previous studies, which indicated that depression, anxiety, and attitude toward medication in general showed the expected association to adherence (Crawshaw et al., 2016; Cully et al., 2006; DiMatteo et al., 2000, Morisky et al., 2008; Shallcross et al., 2015).

Limitations

This study has some limitations that should be discussed. Firstly, a large ceiling effect was confirmed for adherence, perhaps caused by the fact that patients interested in scientific studies are more likely to show more health-related behavior, including higher medication adherence. Since the study was administrated as an online survey, older people especially might

not have been addressed adequately. Considering that non-adherence is even more problematic in the elderly, this could have contributed to a ceiling effect in our sample. Secondly, in the present study, medication adherence was assessed with a self-report measure, and no objective measures were used to record medication use (Lam & Fresco, 2015). Thirdly, the sensitivity and specificity of the theoretically-based cut-off should be examined for each item to evaluate if the cut-off is suitable to detect existing barriers to medication adherence. Using the cut-off, the items could be analyzed with regard to their discriminatory validity to provide evidence of whether the AdRisk items can distinguish between adherent and non-adherent patients. Fourthly, the AdRisk is a self-report measure and therefore vulnerable to conscious and unconscious biases in respondents' answers. We did not control for social desirability (Stirratt et al., 2015).

Conclusion

The AdRisk is one of the first screening instruments to identify a broad non-disease-specific range of barriers to medication adherence in different chronic diseases, preferably before non-adherence occurs. The AdRisk items displayed convergent validity. The subscales and the two total scores of the instrument can be further evaluated to predict adherence.

Clinical Practice

Clinical trials should examine the utility of the AdRisk in various medical and pharmacy practice settings. The AdRisk provides a clinically relevant screening method for non-adherence in patients with different medications and drug regimes. How it can be administrated depends on the disease population and what information is required. It captures many important psychological dimensions to adherence monitoring and can be a useful tool to encourage better communication between patients and their caregiver. Busy practitioners should be able to use all or single items with minimal effort. It is an easy-to-use and inexpensive tool for screening adherence, with the potential for regular self-administration.

The AdRisk can diagnose and potentially resolve different types of barrier to medication adherence and facilitating factors. However, it can also be used to identify patients' concerns that require particular awareness/attention and serve as a basis for tailored interventions to enhance/support patients' adherence. After the identification of potential barriers, tailored interventions are necessary to support the patient in his/her adherent behaviors.

Conflicts of interest

All authors declare no conflict of interest.

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Appendencies

Appendix 1

AdRisk items and distribution of item responses.

Item	Never *n* (%)	Rarely *n* (%)	Sometimes *n* (%)	Often *n* (%)	Always *n* (%)
1. Innerhalb der letzten 4 Wochen habe ich die Medikamente zur Behandlung meiner chronischen Erkrankung so eingenommen, wie sie mir von meinem Arzt verordnet wurden. [*Engl.* During the past four weeks, I have taken my medications as prescribed by my doctor.]	5 (0.7)	13 (1.9)	16 (2.4)	96 (14.2)	547 (80.8)
Item	Strongly disagree *n* (%)	Disagree *n* (%)	Neither *n* (%)	Agree *n* (%)	Strongly agree *n* (%)
2. Durch mein Verhalten kann ich den Verlauf meiner Erkrankung beeinflussen. [*Engl.* What I do can influence the course of my disease.]	23 (3.4)	51 (7.5)	78 (11.5)	343 (50.7)	182 (26.9)
3. Durch eine Behandlung kann die Erkrankung positiv beeinflusst werden. [*Engl.* My treatment is able to have a positive influence on my disease.]	6 (0.9)	19 (2.8)	47 (6.9)	375 (55.4)	230 (34.0)
4. Ich kann akzeptieren, dass ich eine chronische Erkrankung habe. [*Engl.* I can accept living with a chronic disease.]	26 (3.8)	68 (10.0)	58 (8.6)	311 (45.9)	214 (31.6)
5. Ich fühle mich gut darüber informiert, warum ich meine Medikamente nehmen muss. [*Engl.* I feel well informed on why I must take my medications.]	18 (2.7)	38 (5.6)	42 (6.2)	273 (40.3)	306 (45.2)

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6. Ich fühle mich gut darüber informiert, wie und wann ich meine Medikamente nehmen muss. [*Engl.* I fell well informed on how and when I must take my medications.]	8 (1.2)	25 (3.7)	30 (4.4)	272 (40.2)	342 (50.5)
7. Ich kann meine Medikamente so einnehmen, wie ich es mit meinem Arzt besprochen habe. [*Engl.* I'm confident that I can take my medications in the way specified by my doctor.]	4 (0.6)	15 (2.2)	25 (3.7)	268 (39.6)	365 (53.9)
8. Mein Gesundheitszustand hängt von der regelmäßigen Einnahme meiner Medikamente ab. [*Engl.* My health depends on the regular intake of my medications.]	10 (1.5)	40 (5.9)	65 (9.6)	309 (45.6)	253 (37.4)
9. Die Nebenwirkungen der medikamentösen Behandlung machen mir Sorgen. [*Engl.* I'm concerned about the medical treatment's side effects.]	51 (7.5)	134 (19.8)	98 (14.5)	243 (35.9)	151 (22.3)
10. Ich fühle mich von meinem Arzt ausreichend über meine Erkrankung und Behandlungsmöglichkeiten informiert. [*Engl.* I feel sufficiently informed about my disease and possible ways of treatment by my doctor.]	30 (4.4)	92 (13.6)	99 (14.6)	276 (40.8)	180 (26.6)
11. Meine Bedenken und Sorgen werden von meinem Arzt verstanden und ernst genommen. [*Engl.* My doctor understands and takes my concerns seriously.]	37 (5.5)	79 (11.7)	99 (14.6)	272 (40.2)	190 (28.1)
12. In den letzten 2 Wochen habe ich mich häufig niedergeschlagen, depressiv oder hoffnungslos gefühlt. [*Engl.* During the past two weeks, I often felt down, depressed or hopeless.]	104 (15.4)	151 (22.3)	116 (17.1)	213 (31.5)	93 (13.7)
13. In den letzten 2 Wochen habe ich mich häufig stark ängstlich gefühlt. [*Engl.* During the past two weeks, I often felt deeply anxious.]	151 (22.3)	206 (30.4)	124 (18.3)	137 (20.2)	59 (8.7)
14. In den letzten 2 Wochen hatte ich häufig das Gefühl, gestresst oder angespannt zu sein. [*Engl.* During the past two weeks, I often felt tense or stressed.]	52 (7.7)	116 (17.1)	73 (10.8)	307 (45.3)	129 (19.1)
15. Ich nehme Medikamente grundsätzlich so, wie sie mir vom Arzt verordnet wurden. [*Engl.* I generally take medications in the way prescribed by the doctor.]	5 (0.7)	36 (5.3)	29 (4.3)	333 (49.2)	274 (40.5)

16. Im Allgemeinen stehe ich Medikamenten kritisch gegenüber. [*Engl.* I'm generally skeptical when it comes to medications.]	58 (8.6)	149 (22.0)	128 (18.9)	249 (36.8)	93 (13.7)

Notes. Original German wording for the instruments' items is displayed; English wording corresponds to an ad-hoc translation. There is no official translation of the screening instrument at this point. The German wording for the five-point scale is: 'nie' (never), 'selten' (rarely), 'manchmal' (sometimes), 'oft' (often), 'immer' (always) for item one and 'trifft überhaupt nicht zu' (strongly disagree), 'trifft nicht zu' (disagree), 'weder noch' (neither), 'trifft zu' (agree), 'trifft voll und ganz zu' (strongly agree) for items 2-16. AdRisk = Adherence Risk Profile; n=677.

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Appendix 2

Influencing factors for medication adherence that are assessed by the AdRisk items. The table also includes the validation scale and its reported internal consistency.

AdRisk item	Assessed influencing factor	Validation scale	Internal consistency[a] (α)
1	Actual medication adherence	MARS (Mahler et al., 2010)	.79
2	Perceived controllability	IPQ personal control (Gaab, Bunschoten, Sprott, & Ehlert, 2004)	.85
3	Perceived treatability	IPQ treatment control (Gaab, Bunschoten, Sprott, & Ehlert, 2004)	.61
4	Illness acceptance	AIS (Felton & Revenson, 1984)	.80
5	Satisfaction with information about medicines 1	SIMS action and usage (Mahler et al., 2009)	.85
6	Satisfaction with information about medicines 2	SIMS action and usage (Mahler et al., 2009)	.85
7	Self-efficacy for appropriate medication use	SEAMS (Risser et al., 2007)	.91
8	Attitude toward own medication	BMQ specific-necessity (Mahler et al., 2012)	.89
9	Concerns about side effects	BMQ specific-concerns (Mahler et al., 2012)	.83
10	Physician-patient interaction (cognitive)	FAPI (Bieber et al., 2011)	.97
11	Physician-patient interaction (emotional)	FAPI (Bieber et al., 2011)	.97
12	Depression	PHQ-9 (Löwe et al., 2004)	.88
13	Anxiety	GAD-7 (Löwe et al., 2008)	.90
14	Level of perceived stress	PSS-10 (Klein et al., 2016)	.90
15	Past adherence behavior	RAI (Glombiewski et al., 2012)	.74
16	Attitude toward medication in general	BMQ general overuse, general harm (Mahler et al., 2012)	.79

Note. [a] Internal consistency found in the sample for this study.

Studie 2 (Manuskript): Validierung AdRisk

Appendix 3

Further information on sample characteristics.

	n (%)
Demographics	
Marital status	
Single	143 (21.1)
In a relationship	144 (21.3)
Married	310 (45.8)
Divorced	65 (9.6)
Widowed	15 (2.2)
Highest education qualification	
Volksschule (~ 8 years of school)	13 (1.9)
Hauptschule (~ 9 years of school)	62 (9.2)
Realschule (~10 years of school)	132 (19.5)
(Fach) Abitur (~ 12–13 years of school)	97 (14.3)
Vocational training	237 (35.0)
Bachelor's degree	39 (5.8)
Master's degree	62 (9.2)
Higher university degree	33 (4.9)
No degree	2 (0.3)
Occupational status	
School student	3 (0.4)
University student	49 (7.2)
Employee (full time)	190 (28.1)
Employee (part time)	125 (18.5)
Home maker	22 (3.2)
Retired	193 (28.5)
Unemployed	29 (4.3)
Certified sick	40 (5.9)
Other[b]	26 (3.8)
Disease-related information	
Number of comorbidities	
Mean ± SD	2.4 ± 1.8
Range	0–12
Number of further medications	
Mean ± SD	3.0 ± 2.4
Range	1–15

Notes. [b] Other occupations indicated were: 450 – Euro Job (minor employment, 6), trainee in the scope of vocational training (10), parental leave (8), socio-professional reintegration money (1) and occupational retraining (1). n=677.

Studie 2 (Manuskript): Validierung AdRisk

Appendix 4

Correlations between the AdRisk items and the MARS-D score.

Item	MARS-D	*r*	95 % CI
1[a]		-.483**	[-.535, -.419]
2[a]		-.089*	[-.167, -.005]
3[a]		-.152**	[-.226, -.075]
4[a]		-.159**	[-.236, -.085]
5[a]		-.188**	[-.260, -.111]
6[a]		-.183**	[-.252, -.112]
7[a]		-.336**	[-.405, -.263]
8[a]		-.222**	[-.291, -.142]
9		-.117**	[-.193, .-035]
10[a]		-.225**	[-.291, -.155]
11[a]		-.200**	[-.267, -.131]
12		-.037	[-.116, .039]
13		-.026	[-107., .050]
14		-.069*	[-.148, .006]
15[a]		-.487**	[-.544, -.421]
16		-.047	[-.127, .033]

Notes. Spearman correlation coefficients (*r*) are displayed. Bootstrap confidence intervals are indicated. Method: percentile, 1,000 samples; CI = confidence interval; * $p < .05$, ** $p < .01$, one-tailed; $n = 677$. [a] Reverse coded items.

A. 3 Studie 3

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Studie 3 (Manuskript): Prädiktoren Adhärenz

Psychological predictors of fluctuations in medication adherence in various chronic conditions

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Studie 3 (Manuskript): Prädiktoren Adhärenz

Abstract

Objective. Non-adherence is a persistent problem in various chronic clinical conditions linked to adverse health outcomes and higher health care cost. Psychological barriers to adherence have often been neglected. We aim to investigate which psychological predictors of non-adherence can explain incremental variance in fluctuations of current medication adherence (after four weeks) beyond previous medication adherence.

Methods. This secondary analysis used data from the "AdRisk" validation study. In total, 677 patients with chronic conditions (diabetes, hypertension, COPD, epilepsy, rheumatoid arthritis, and Crohn's disease) completed an online survey assessing the physician–patient interaction, satisfaction with information about medicine, anxiety, depression, stress, self-efficacy for medication use, beliefs about medicines, illness perception, illness acceptance, and medication adherence. After four weeks, 400 of the participants completed a second survey about their current adherence.

Results. Age (standardized coefficient β = . 06, p = . 0.01), previous adherence at baseline (β = . 24, p < . 0.01), the quality of the physician–patient interaction (β = . 08, p < . 0.01), stress (β = . 16, p < . 0.01), self-efficacy for appropriate medication use (β = . 25, p = . 0.01), and adherence as a behavior pattern (β = -. 29, p < . 0.01) were positively associated with current adherence in the second assessment, while satisfaction with information about medicine (β = -. 08, p < . 0.01) and anxiety (β = -. 29, p < . 0.01) were negatively associated.

Conclusion. Several psychological risk factors predict intra-individual fluctuations for non-adherence after four weeks, beyond the explained variance by previous medication adherence.

Keywords: adherence, prediction, intra-individual fluctuation, chronic diseases, path analysis

Background

Non-adherence to medical treatment, especially in chronic clinical conditions, is one of the most difficult challenges in health care. An examination of reviews indicates that non-adherence rates have constantly been high over the last decades, varying slightly depending on the disease (van Dulmen et al., 2007). As a consequence, numerous patients did not get the maximum benefit of their medical treatment (van Dulmen et al., 2007), leading to deteriorated health outcomes, reduced quality of life, and higher health care costs (Osterberg & Blaschke, 2005; Sabaté, 2003). Up to now, different theoretical approaches have been used to solve the adherence problem. The multidimensional model of adherence by the World Health Organization (WHO) gives a comprehensive overview of different factors influencing adherence in general (Sabaté, 2003). The Health Belief Model (Rosenstock, 1974) as well as the Common Sense Model of Self-Regulation (Leventhal & Ian, 2012) were often used to explain health behavior. Complementarily, the Necessity–Concerns Framework considers patients' individual beliefs about the necessity and concerns of the prescribed medication and treatment (Horne et al., 2013).

Reviews indicate a multitude of factors promoting adherence (Capoccia, Odegard, & Letassy, 2016; van Dulmen et al., 2007; Vrijens, Antoniou, Burnier, de la Sierra, & Volpe, 2017). Most attempts to improve adherence aimed at practicability, application of skills, or tried to use modern reminder systems and new technologies (Kripalani, Yao, & Haynes, 2007; Schroeder, Fahey, & Ebrahim, 2004). However, these approaches typically neglect psychological barriers leading to non-adherent behavior (Arlt, Nestoriuc, & Rief, 2017). Therefore, research has focused on emotional factors (especially stress, depression, and anxiety) (Morisky, 2008) and cognitive factors such as beliefs about medicines and treatment or illness to predict medication adherence (Osterberg & Blaschke, 2005). Studies indicate that lower concerns about medicines' side effects and a higher perceived necessity are associated with better adherence (Bardel, Wallander, & Svärdsudd, 2007; Glombiewski, Nestoriuc, Rief, Glaesmer, & Braehler, 2012). In addition, studies refer to low self-efficacy being associated with non-adherence (Colbert, Sereika, & Erlen, 2013; Luszczynska, Sarkar, & Knoll, 2007). Self-efficacy for medication use is especially important concerning adherence. It can be described as the personal belief of one's own ability and competence to keep at one's treatment regimen as expected and desired (Krueger, Berger, & Felkey, 2005). Providing patients with sufficient information about their prescribed medication is an essential precondition for understanding its utility as well as using it appropriately (Bourbeau & Bartlett, 2008; Horne, Hankins, & Jenkins, 2001). The relevance of the patient–practitioner interaction has often been confirmed, with a trust and support relationship leading to better adherence (Krueger et al., 2005; Osterberg & Blaschke, 2005). Previous studies indicate that a lower level of illness acceptance is associated with reduced quality of life and higher health care utilization (Janowski, Kurpas, Kusz, Mroczek, & Jedynak, 2013; Kurpas et al., 2013). However, there is a lack of research on the association of illness acceptance with adherence. In a study with hypertension patients, a higher illness acceptance contributed to higher non-

pharmacological therapy, but not to medication adherence (Jankowska-Polańska, Blicharska, Uchmanowicz, & Morisky, 2016).

Previous adherence behavior is commonly considered as a good predictor of future behavior (Rief & Nestoriuc, 2015). In a prospective longitudinal study, past medication adherence (measured via refill behavior) predicted future refill behavior (Molfenter, Bhattacharya, & Gustafson, 2012). In a representative German study, non-adherence was found to be widespread within the general population (Glombiewski et al., 2012). Moreover, 33% of the participants in the study stated having been repeatedly non-adherent in the past. The authors concluded that the general tendency to be (non-) adherent can thus be assumed as a relatively stable behavior pattern in the general population. Furthermore, the time course indicates that adherence rates among patients with chronic conditions drop dramatically after the first six months of the treatment (Osterberg & Blaschke, 2005). Moreover, patients have to handle different situational contexts that can support or disrupt the disease management in daily life (Mulvaney et al., 2012). Further, there is evidence that intra-individual fluctuations to daily adherence exist (Berg et al., 2014). These distinctions are caused by differences in self-regulatory abilities (Berg et al., 2014). The identification of intra-individual reasons for sudden changes in adherence might be an important step to understand the underlying mechanisms of growing non-adherence. This could be helpful to generate individualized prediction models (Hugtenburg, Timmers, Elders, Vervloet, & van Dijk, 2013), which allow to address these mechanisms via multidimensional and systematically tailored interventions.

Therefore, more research into causes of sudden changes in adherence is needed in order to identify pathways that can be addressed in future interventions. The aim of the present longitudinal study was to identify psychological predictors of non-adherence that can explain incremental variance in fluctuations of current adherence (four weeks).

Methods

Sampling

The study was approved by the Ethics Committee of the Department of Psychology of the University of Marburg (Germany). This secondary analysis used data from the validation study of the Adherence Risk Profile (AdRisk) questionnaire (currently submitted). Data collection was carried out online via Unipark (QuestBack GmbH, Germany) from September 2017 to March 2018. Flyers including the link directing to the site were distributed via mailing lists of the University of Marburg, social media, and an announcement in a local newspaper, and via pharmacies and general practitioners, in the University Hospital of Marburg and Giessen (UKGM), patient organization websites, and support groups for patients. Participants had the chance to win one of four vouchers (50 euros each) for an online store.

The study was composed of two parts. In part one, participants were informed about the purpose of the study and could click a button to give their informed consent. Subsequently, they were asked to give demographic information (age, gender, marital status, nationality, and monthly net household income), as well as information concerning disease and therapy (chronic disease and duration, number of medicines, number and name of other diseases and medicines). Afterwards, participants answered questionnaires (see measures). The participants received a link to a second, unrelated web-based survey to provide their e-mail address to ensure anonymity at the end of the questionnaire. In part two, four weeks later, participants received an invitation to the second survey.

A total of 823 participants provided their informed consent. Of these, 132 were excluded due to missing data, and eight were excluded due to implausible data. Another six participants dropped out because of duplicated data (N=4) and a survey completion time of less than 10 minutes (N=2). The remaining 677 participants were checked for inclusion criteria and plausibility of answers and were all included in the study. A total of 565 participants were registered for the second survey, of whom 468 provided informed consent for part two, in which 14 participants were excluded because of double cases. In sum, 400 participants could be assigned to parts one and two of the survey by their individual code (86% of patients with informed consent), while four were excluded because of missing data.

Measures

Medication Adherence (MARS-D). Medication adherence was assessed using the validated German version of the Medication Adherence Report Scale (MARS-D; Mahler et al., 2010) The MARS-D is a five-item self-report scale. The items are statements of non-adherent behavior on which patients have to rate their behavior on a five-point Likert scale, ranging from 1=always to 5=never. Therefore, a higher score indicates a higher medication adherence. The internal consistency of the MARS-D ranges from Cronbach's α = .69 to .90 (Mahler et al., 2010).

Quality of the Physician–Patient Interaction (FAPI). In order to assess the quality of the physician–patient interaction, the validated German version of the Questionnaire on the Quality of Physician-Patient Interaction (QQPPI; German: Fragebogen zur Arzt-Patient-Interaktion - FAPI) was used (Bieber et al., 2006). The QQPPI is a 14-item self-assessment questionnaire. Patients rate their agreement with statements about the interaction with their physician on a five-point scale. The total score is calculated as the average of all 14 items, ranging from 1 to 5. Higher scores indicate a better quality of physician–patient interaction. This questionnaire shows a good internal consistency with a Cronbach's α = .95.

Satisfaction with Information about Medicine Scale (SIMS-D). The German version of the Satisfaction with Information about Medicines Scale (SIMS-D; Mahler et al., 2009) was used to measure satisfaction with information about medicines. Participants were asked to rate the information received about several aspects of their medicines (e.g., "What your medicine is for.") on a five-point scale: too much, about right, too little, none received, and none needed. For the work at hand, only subscale 1 (items 1–9) assessing satisfaction with information about action and usage of medication is of relevance. Higher subscale scores indicate higher satisfaction. Previous research's internal consistency for subscale 1 was shown to be good (α = .87; Mahler et al., 2009).

Generalized Anxiety Disorder Scale (GAD-7). The German version of the seven-item Generalized Anxiety Disorder Scale (GAD-7; Löwe et al., 2008) was used to assess anxiety severity. Core symptoms of generalized anxiety disorder are described (e.g., "Feeling nervous, anxious, or on edge"), and participants were asked to indicate how often during the past two weeks they have been bothered by each of the symptoms (four-point scale ranging from 0 [not at all] to 3 [nearly every day]). The resulting sum score is used as an indicator for anxiety symptom levels, with higher scores representing higher levels of anxiety. The German version of the scale showed a good internal consistency (α = .89).

Patient Health Questionnaire (PHQ-9). The German version of the Patient Health Questionnaire (PHQ-9; Löwe, Kroenke, Herzog, & Gräfe, 2004) was used to assess depression

severity. The PHQ-9 comprises nine items asking for the frequency at which participants have been bothered with symptoms of depression during the past two weeks (e.g., "Feeling down, depressed or hopeless") on a four-point scale from 0 (not at all) to 3 (nearly every day). Summing up those nine items leads to a total score, with higher values indicating higher depression severity. A tenth item asks for the patients` overall rating of symptom-related impairment. The German version of the scale showed good internal consistency in a previous study (α = .88; Löwe et al., 2004).

Perceived Stress Scale (PSS). The level of perceived stress was assessed using the German version of the Perceived Stress Scale (PSS-10; Klein et al., 2016). The PSS-10 consists of 10 items (e.g., "In the last month, how often have you felt nervous and 'stressed'?"), which have to be rated on a five-point scale from 0 (never) to 4 (very often). Higher levels of perceived stress are represented by higher sum scores. In previous research, internal consistency for the overall scale was good (α = .84; Klein et al., 2016).

Self-Efficacy for Appropriate Medication Use Scale (SEAMS). The Self-Efficacy for Appropriate Medication Use Scale (SEAMS) is a validated 13-item self-report scale (Risser, Jacobson, & Kripalani, 2007). Participants are asked to state their level of confidence about taking their medication correctly under the described circumstances on a three-point Likert scale (1="not confident", 2="somewhat confident", 3="very confident"). Higher scores indicate a higher level of self-efficacy for medication intake. The internal consistency of the SEAMS is good with Cronbach's α = .89.

Beliefs about Medicines Questionnaire (BMQ). The Beliefs about Medicines Questionnaire (BMQ) is a validated 18-item self-assessment questionnaire assessing individual attitudes towards medication (Horne, Weinman, & Hankins, 1999). It is divided into two sections, each comprising two subscales. The first section (BMQ-Specific) assesses patients' personal beliefs about their prescribed medication. The subscale Specific-Necessity assesses patients' beliefs about their personal need and the importance of the medication. The subscale Specific-Concern addresses beliefs about possible side effects. The second section (BMQ-General) assesses beliefs about medicines in general. It contains the subscale General-Harm that focuses on the beliefs that medication in general can be harmful. The subscale General-Overuse covers the beliefs that medication in general is used and prescribed too often. All items are rated on a five-point Likert scale, ranging from 1=strongly disagree to 5=strongly agree. Higher scores in the Specific-Necessity Scale indicate a stronger belief on personal needs for the prescribed medication. In the Specific-Concerns Scale, higher scores reflect stronger concerns about potential negative effects of the medication. Higher scores for the General-Harm and General-Overuse Scales indicate a more negative view of medication in general for the former, and a

negative notion concerning overuse of medication for the latter. The internal consistency ranges from Cronbach's α = .79 to .83.

Rief Adherence Index (RAI). The Rief Adherence Index (RAI) (Glombiewski et al., 2012) was used to assess adherence as a behavior pattern and independent of current medication intake. The scale consists of four items describing adherence-related behaviors of the past (e.g., "I discontinued my medication earlier than recommended by the doctor"), which have to be rated on a five-point scale ranging from 1 ([almost] never happened [in 0–20% of cases]) to 5 ([almost] always happened [in 80–100% of cases]). In order to obtain a general behavior pattern, participants were instructed to take into account "all past behaviours concerning any prescribed medication'' (Glombiewski et al., 2012). Higher RAI sum scores reflect higher general non-adherence in the past. The scale showed satisfactory internal consistency (α = .79) (Glombiewski et al., 2012).

Illness Perception Questionnaire- revised (IPQ-r). The scales of the German version of the Illness Perception Questionnaire – revised (IPQ-R; Broadbent, Petrie, Main, & Weinman, 2006; Glattacker, Bengel, & Jaeckel, 2009) were used to assess personal control and treatment control. The two subscales each consist of four items. IPQ-R scales personal control (e.g., "There is a lot which I can do to control my symptoms.") and treatment control (e.g., "The negative effects of my illness can be prevented (avoided) by my treatment."). Participants had to rate their approval of the statements on a five-point scale, ranging from 1 (strongly disagree) to 5 (strongly agree). Higher mean scores represent the experience of higher personal control and higher treatment control, respectively. In a first psychometric evaluation of the German version, the scales had good internal consistencies (α = .80 each).

Acceptance of Illness Scale (AIS). The Acceptance of Illness Scale (AIS; Felton, Revenson, & Hinrichsen, 1984) was translated into German by two experienced researchers in the field fluent in both languages. A final version was developed comparing both translations. The scale consists of eight items (e.g. "I have problems with adapting to limitations imposed by my illness."), which have to be rated on a five-point scale from 1 (strongly agree) to 5 (strongly disagree). A score is obtained by summing up the items, with a higher score representing higher acceptance of illness. The internal consistency was good (α = .82; Felton et al., 1984).

Data Analysis

The analyses were conducted using the statistic software SPSS-25 (IBM) and Mplus-7.2 (Muthén & Muthén, 2012). In consideration of the theoretical background of psychological barriers of adherence, path analyses with maximum likelihood estimation were selected as an appropriate method. Current adherence assessed via the MARS-D after four weeks served as a dependent variable in the research model (Figure 1). Additionally, 21 independent variables were divided into three categories: demographics, health- and treatment-related factors, and patient-related factors (psychological symptoms, behavioral and treatment beliefs, cognitive and emotional representation). The large number of participants allowed the consideration of this large group of variables. All variables were used as manifest variables. The path coefficients of the prediction variables (independent variables) on current adherence (dependent variable) were estimated.

Results

Path analyses were based on the data of 677 participants. The demographic characteristics of the sample are illustrated in Table 1.

Table 1

Demographic Characteristics of the Total Sample (N=677)

Variable	***N***	***Result***
Sex; female, %	*523*	*77.3*
Age; years	*677*	*46.04 (14.62)*
Relationship; yes, %	*454*	*67.1*
Nationality; German, %	*639*	*94.4*
Income (monthly net household income); n=677, %		
< 750 euros per month	*78*	*11.5*
750 up to < 1,250 euros per month	*141*	*20.8*
1,250 up to < 2,000 euros per month	*192*	*28.4*
≥ 2,000 euros per month	*266*	*39.3*
Chronic disease; %		
Diabetes mellitus type 2	*60*	*8.9*

Hypertension	*87*	*12.9*
Chronic obstructive pulmonary disease	*140*	*20.7*
Rheumatoid arthritis	*149*	*22.0*
Epilepsy	*70*	*10.3*
Crohn´s disease	*171*	*25.3*
Time since medical treatment; years	*677*	*7.68 (0.73)*
Number of prescribed medications	*677*	*2.62 (1.72)*
Time since diagnosis; years, %	*677*	*10.62 (10.26)*
Comorbidity	*439*	*2.4 (1.82)*
Previous adherence (MARS-D-T0)	*677*	*22.68 (2.67)*
Quality of the physician–patient interaction (FAPI)	*677*	*40.68 (15.45)*
Satisfaction with information about medicine (SIMS-D)	*677*	*9.29 (4.92)*
Anxiety (GAD)	*677*	*7.06 (5.10)*
Depression (PHQ)	*677*	*9.67 (5.91)*
Stress (PSS)	*677*	*19.80 (7.46)*
Self-efficacy for appropriate medication use (SEAMS)	*677*	*37.82 (7.14)*
Specific-necessity (BMQ-sn)	*677*	*20.89 (3.78)*
Specific-concerns (BMQ-sc)	*677*	*14.38 (5.06)*
General-harm (BMQ-gh)	*677*	*8.47 (3.44)*
General-overuse (BMQ-go)	*677*	*12.63 (3.56)*
Adherence (behavior pattern) (RAI)	*677*	*6.64 (2.77)*
Personal control (IPQ-pc)	*677*	*13.84 (3.44)*
Treatment control (IPQ-tc)	*677*	*11.97 (2.72)*
Illness acceptance (AIS)	*677*	*24.76 (6.57)*
Current adherence (MARS-D-T1)	*400*	*22.33 (2.77)*

Note. Mean (SD) unless otherwise noted. SD = standard deviation; MARS-D = German version of the Medication Adherence Report Scale; FAPI = Engl. QQPPI, Questionnaire on the Quality of Physician–Patient Interaction; SIMS-D = German version of the Satisfaction with Information about Medicines Scale; GAD-7 = Seven-item Generalized Anxiety Disorder Scale; PHQ-9 = Nine-item Patient Health Questionnaire; PSS-10 = 10-item Perceived Stress Scale; SEAMS = Self-Efficacy for Appropriate Medication Use Scale; BMQ = Beliefs about Medicines Questionnaire; RAI = Rief Adherence Index; IPQ-R = Illness Perception Questionnaire – revised; AIS = Acceptance of Illness Scale.

Model Fit. A maximum log-likelihood (MLR) was calculated with Mplus-7.2 (Muthén & Muthén, 2012) (see Figure 1 for the path diagram using standardized path coefficients) in order to test the model fit. The model fit the data well. The χ^2 was significant, χ^2 (21) = 549.56, p < 0.001. The CFI was 1.00, and the RMSEA was 0.00. The model explained 84.8% of the variance.

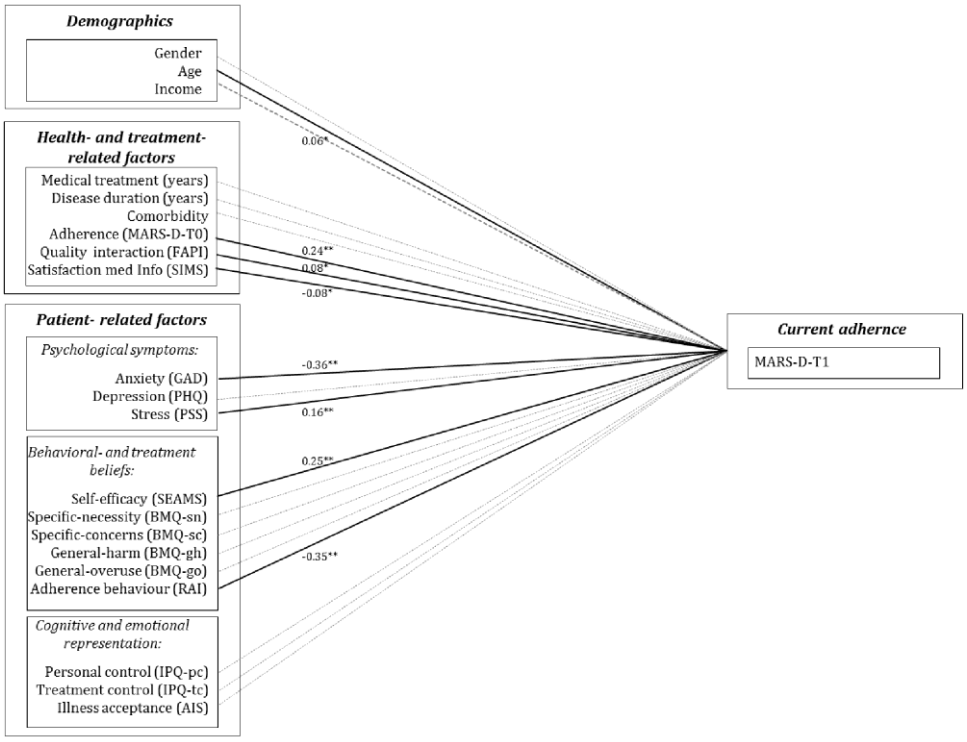

Figure 1. Path analyses, calculated with maximum likelihood estimation, with all path coefficients standardized (ß). The model displays prediction variables on short-term adherence. All variables were manifest. Significant paths (*p<.05, **p<.001) are presented. MARS-D = German version of the Medication Adherence Report Scale; FAPI = Engl. QQPPI, Questionnaire on the Quality of Physician–Patient Interaction; SIMS-D = German version of the Satisfaction with Information about Medicines Scale; GAD-7 = Seven-item Generalized Anxiety Disorder Scale; PHQ-9 = Nine-item Patient Health Questionnaire; PSS-10 = 10-item Perceived Stress Scale; SEAMS = Self-Efficacy for Appropriate Medication Use Scale; BMQ = Beliefs about Medicines Questionnaire; RAI = Rief Adherence Index; IPQ-R = Illness Perception Questionnaire – revised; AIS = Acceptance of Illness Scale.

Path Analysis. The results of the path analysis are illustrated in Table 2. Age (β = . 06, p = . 0.01), previous adherence (at baseline) (β = . 24, p < . 0.01), the quality of the physician–patient interaction (β = . 08, p < . 0.01), stress (β = . 16, p < . 0.01), self-efficacy for appropriate medication use (β = . 25, p = . 0.01), and adherence as a behavior pattern (β = -. 29, p < . 0.01)

were positively associated with current adherence in the second assessment. The satisfaction with information about medicine (β = -. 08, p < . 0.01) and anxiety (β = -. 29, p < . 0.01) was negatively associated with current adherence.

Table 2

Path Coefficients and P-Values of the Prediction Variables on Current Adherence

Prediction Variables (Independent Variables)	***Adherence (Dependent Variable)***				
	ß	**B**	**SE**	***p***	
Gender	*0.01*	*0.11*	*0.24*	*0.66*	
Age	*0.06*	*0.02*	*0.01*	*0.01*	*
Income	*-0.02*	*-0.09*	*0.12*	*0.45*	
Medical treatment (years)	*-0.03*	*-0.23*	*0.16*	*0.15*	
Time since diagnosis (years)	*0.01*	*0.01*	*0.01*	*0.56*	
Comorbidity	*0.02*	*0.03*	*0.08*	*0.70*	
Previous adherence (MARS-D-T0)	*0.24*	*0.42*	*0.06*	*0.00*	**
Quality of the physician–patient interaction (FAPI)	*0.08*	*0.03*	*0.01*	*0.00*	*
Satisfaction with information about medicine (SIMS-D)	*-0.08*	*-0.08*	*0.01*	*0.00*	*
Anxiety (GAD)	*-0.29*	*-0.16*	*0.03*	*0.00*	**
Depression (PHQ)	*-0.02*	*-0.02*	*0.04*	*0.61*	
Stress (PSS)	*0.16*	*0.11*	*0.03*	*0.00*	**
Self-efficacy for appropriate medication use (SEAMS)	*0.25*	*0.07*	*0.03*	*0.01*	*
Specific-necessity (BMQ-sn)	0.03	*0.04*	*0.04*	*0.26*	
Specific-concerns (BMQ-sc)	-0.02	*-0.02*	*0.03*	*0.48*	
General-harm (BMQ-gh)	0.03	*0.04*	*0.05*	*0.41*	
General-overuse (BMQ-go)	-0.03	*-0.05*	*0.04*	*0.23*	
Adherence (behavior pattern) (RAI)	-0.35	*-0.43*	*0.06*	*0.00*	**
Personal control (IPQ-pc)	0.01	*0.02*	*0.06*	*0.82*	
Treatment control (IPQ-tc)	0.01	*0.01*	*0.06*	*0.82*	
Illness acceptance (AIS)	-0.03	*-0.02*	*0.02*	*0.34*	

Note. The table shows standardized (ß) and unstandardized (B) path coefficients and the p-values for the significance test (*p<.05, **p<.001) of the prediction variables on adherence (measured via the MARS-D). MARS-D = German version of the Medication Adherence Report Scale; FAPI = Engl. QQPPI, Questionnaire on the Quality of Physician–Patient Interaction; SIMS-D = German version of the Satisfaction with Information about Medicines Scale; GAD-7 = Seven-item Generalized Anxiety Disorder Scale; PHQ-9 = Nine-item Patient Health Questionnaire; PSS-10 = 10-item Perceived Stress Scale; SEAMS = Self-Efficacy for Appropriate Medication Use Scale; BMQ = Beliefs about Medicines Questionnaire; RAI = Rief Adherence Index; IPQ-R = Illness Perception Questionnaire – revised; AIS = Acceptance of Illness Scale.

Discussion

We present one of the first studies to predict intra-individual fluctuation in adherence with mainly psychological variables in different chronic conditions after four weeks. Current adherence was predicted by previous adherence, non-adherent behavior patterns, age, quality of the physician–patient interaction, satisfaction with information about medicine, anxiety, stress, and self-efficacy for appropriate medication use.

Previous reviews illustrate the importance of unifying predictors of non-adherence (Capoccia et al., 2016; van Dulmen et al., 2007; Vrijens et al., 2017). Allemann, Nieuwlaat, van den Bemt, Hersberger, and Arnet (2016) explained that it is essential to differentiate between modifiable and unmodifiable determinants in regards to the selection of interventions enhancing adherence. They emphasized the relevance for clinical practice to tailor interventions for unmodifiable determinants, such as age, gender, and income (Allemann et al., 2016). In addition, interventions should target current modifiable determinants, such as knowledge, skills, or beliefs (Allemann et al., 2016). The relevance of tailored interventions to adapt the needs of the patients was also expressed by others (Hugtenburg et al., 2013; Müller, Kohlmann, & Wilke, 2015). Nevertheless, another promising path could be a more precise consideration of psychological predictors that could lead to intra-individual fluctuations in adherence. There are first indications that these fluctuations can be explained through differences in goal planning (Wiebe, Baker, Suchy, Stump, & Berg, 2018), such as the perceived self-regulation of the patients (Berg et al., 2014).

Not surprisingly, previous adherence and baseline adherence as a behavior pattern predict adherence four weeks later. Previous research shows that non-adherence rates are relatively stable (Osterberg & Blaschke, 2005). Nevertheless, the influence is not gigantic, which emphasizes the relevance of this study to consider other important predictors, such as the quality of the physician–patient interaction, satisfaction with information about medicine, and self-efficacy for appropriate medication use.

A better quality of the physician-patient interaction was associated with a higher adherence. The quality is a very important factor to improve adherence to treatment recommendations in several chronic conditions (Vangeli et al., 2015; Zolnierek & DiMatteo, 2009). Moreover, satisfaction with information about medicine was negatively associated with current adherence. This is in accord with the research showing that providing patients with sufficient information about their prescribed medication is an essential precondition for

understanding its utility as well as using it appropriately (Bourbeau & Bartlett, 2008). Furthermore, self-efficacy is one of the most prominent determinants to enhance adherence (Holmes, Hughes, & Morrison, 2014). Our results are in line with various studies that found low self-efficacy beliefs were correlated to non-adherence in patients with various chronic conditions (Colbert et al., 2013; Houston & Fominaya, 2015; Vangeli et al., 2015). These aspects are clinically highly relevant and should be implemented in the training of physicians and interventions to enhance adherence.

Comorbid diagnoses of anxiety and depression are common in patients with various chronic conditions and lead to reduced quality of life, reduced health outcomes, and more functional impairments (Cully et al., 2006; DiMatteo, Lepper, & Croghan, 2000). In this study, anxiety was negatively associated with current adherence. Further studies provide heterogeneous results suggesting that anxiety might not impact adherence in chronic disease studies in general (DiMatteo et al., 2000). Reasons for this might be due to inconsistent definitions and assessments. In contrast, more recent studies show a clear association of medication non-adherence and a high level of anxiety sensitivity as well as diagnosed anxiety disorders (Alcántara et al., 2014). Moreover, studies have examined the impact of perceived stress on medication adherence in patients with different chronic conditions (Cohen, Janicki-Deverts, & Miller, 2007). A study of patients with epilepsy and hypertension showed that a high level of perceived stress is correlated with poor medication adherence (Morisky, 2008; Shallcross et al., 2015). However, there is no distinction between the different aspects of stress. Thus, an increase of the stress level could lead to more self-attention, which, in turn, could lead to a better adherence. The result that depression has no influence on adherence is contrary to research. Meta-analyses indicate that depression is a risk factor for non-adherence in various chronic diseases, where patients with comorbid depression were two to three times as likely to be non-adherent compared to patients without a diagnosis (Crawshaw, Auyeung, Norton, & Weinman, 2016; DiMatteo et al., 2000). The mean depression scores of this sample were unremarkable, so it is possible that this sample is not representative for persons with a chronic disease and comorbid depression.

There are some limitations of the present study that have to be considered. All data of the study were assessed via self-report online measures. The study seemed to have attracted a homogenous and adherent sample, which might not have been representative of the population of patients suffering from chronic diseases. Our results cannot be transferred to patient groups experiencing serious difficulties in being adherent. In addition, the inclusion criteria, such as diagnoses, prescribed medication, treatment time, and comorbidity, were not externally verified. Secondly, we only used a self-assessment tool for adherence, which might have further

aggravated the bias in adherence scores. However, the MARS-D is a validated and reliable questionnaire, and thus it is likely that patients in our study were more adherent than average. An objective measure as well as a measure that covers social desirability should still be used to confirm our results in the future. Thirdly, every chronic condition presents different challenges and requirements for treatment. Therefore, it is plausible that adherence is not predicted similarly across chronic health conditions (Foot, La Caze, Gujral, & Cottrell, 2016). Furthermore, other concepts may be important to consider, and predictors can differ depending on each phase of medication adherence, initiation, implementation, and persistence (Vrijens et al., 2012).

In conclusion, this study was able to identify several psychological predictors of non-adherence to explain incremental variance in short-term (four weeks) fluctuation of actual medication adherence. Firstly, there are psychological predictors, which were so far neglected in the clinical research, namely the quality of the physician–patient interaction, satisfaction with information about medicine, self-efficacy for appropriate medication use, anxiety, and stress. Secondly, more research into causes of sudden changes in adherence is needed in order to identify pathways that can be addressed in future interventions.

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A. 4 Studie 4

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Expectation-focused online intervention to optimise adherence in patients with type-II diabetes mellitus:

Protocol of a randomised controlled trial

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Contents

1. Abstract

Background: Adherence in type 2 diabetes mellitus (t2dm) is a problem. Adherence to medication, exercise, diet and other aspects of recommended self-care is notoriously problematic in individuals with type 2 diabetes and has been estimated below 50% on average. Recent evidence suggests that online interventions have the potential to enhance self-management in t2dm. This randomised controlled trial evaluates efficacy and specificity as well as the mode of action of a psychological online-intervention (Covivio) aimed at enhancing adherence to medication and life-style changes by targeting expectations about illness and medications in patients with type 2 diabetes.

Methods/Design: A total of 390 patients with type 2 diabetes will be randomised to one of three groups receiving psychological online training focusing on patients' expectation management (*Covivio*), psychological online relaxation training (*Relaxio*), or treatment as usual. Participants will be recruited through general practitioners, diabetes clinics, over the internet, and through ads and flyers. Inclusion criteria include deficient adherence behaviours, willingness to participate in regular primary-care monitoring of glycaemia control and absence of severe mental disorders. Assessments will take place before and after completion of the online training and at 3- and 6-month follow-ups. The primary outcome is patient-reported adherence to diabetes self-care behaviours. Secondary outcomes include objective measures of glycaemia control (HbA1c), diabetes long-term effects and complications, body-mass-index, physical activity, psychological symptoms of anxiety, depression and somatisation. Treatment and illness expectations are investigated as a priori hypothesised mediators.

Discussion: Enhancing diabetic self-management through expectation-focused web-based interventions might be a potential pathway in health care to improve patients' adherence during long-term medication intake. The results will contribute to the scientific literature on evidence-based online interventions for t2dm and potentially broaden the existing repertoire of effective treatment options facilitating adherence in this population.

Keywords: Self-management behaviour, expectations, illness and treatment beliefs, adherence, psychological online-intervention, process-based cbt, diabetes mellitus type 2, RCT

Trial registration: NCT03181737 **Date of registration:** June 9, 2017

2. Background

Diabetes mellitus is widespread. According to the International Diabetes Federation (IDF) estimates from 2018, there are 425 million people living with diabetes worldwide (1). Currently, about 6.7 million people in Germany suffer from diabetes mellitus including about 2 million people who are undetected, and 95 percent of the individuals diagnosed with diabetes suffer from type 2 diabetes mellitus (t2dm) (2).

Adherence is often a problem in diabetes. Good glycaemic control requires a complex set of behaviours and can be summarised with the following five aspects: dietary control, physical activity, regular blood glucose monitoring and medication adherence (3). Reviews indicate that non-adherence has been a persisting challenge over the last decades (3, 4). Adherence to prescribed medication ranged from 36% to 93% for oral hypoglycaemic agents (OHA) and from 62% to 64% for insulin users while adherence to long-term exercise programs can vary between 10% and 80% (5). Previous studies have detected that the recommended glycaemic goals are achieved by less than 50% of patients (5), although there exist various therapy options for different stages of the disease. As a result, hyperglycaemia plus acute and chronic complications increase morbidity and premature mortality and lead to more hospitalisations and higher costs to health services (4).

Cognitive behavioural therapy (CBT) has been demonstrated to be effective for people with diabetes to enhance aspects of adherence behaviour (4). The meta-analyses of randomised controlled trials (RCTs) of psychological interventions showed improvements in long-term glycaemic control and distress but not in weight control or blood glucose concentration. Elements of CBT were among other strategies such as relaxation techniques, problem solving, goal setting, self-monitoring of behaviour and enlisting social support. Most of the interventions examined so far were mostly face-to-face (6) or group settings (7, 8), which might not be an appropriate approach for all individuals with diabetes. Furthermore, there are barriers at the health-care system level such as a limited availability of evidence-based interventions for individuals with diabetes adapted to their needs. In our global world with fast-moving digitisation, online self-help, therapy and lifestyle change interventions are becoming increasingly popular (9). For this reason, interventions to improve adherence using electronic resources seem promising (10).

Online interventions have many advantages over face-to-face interventions. Online interventions can reach a variety of individuals (11), can be used comfortably from home, are flexibility over time and available at any time, 24 hours a day (12). Further advantages are the

anonymity and the possibility to present complex information in the form of videos or vivid graphics that are easy to understand (13). Regular updates that bring the program up to date in a short time are also beneficial. In addition, it is possible to implement interactive elements so that an individualised intervention is avoided (14).

Meta-analyses have shown that internet-based cognitive-behavioural interventions (ICBT) are effective in treating different chronic somatic conditions such as tinnitus, epilepsy and chronic pain (15). A review by Ramadas and colleagues (16) indicated that interactive interventions are effective for patients with t2dm. Examples of such interactive elements are goal setting, immediate feedback, the implementation of self-control and chat rooms for exchange with other stakeholders (17). Education about diabetes and consequences of the disease as well as relaxation techniques such as imagination techniques, breathing and physical exercises (i.e. autogenic training and progressive muscle relaxation) are types of interventions which can lead to an improvement of glycaemic control (7). Taking into account that treatment adherence to internet-based interventions is a problem (18), Kelders and colleagues (19) propose the use of reminder systems (daily text messages or phone calls) to increases adherence.

There is evidence that patients' expectations can be influenced by psychological interventions (20). These types of interventions focus on the cognitive representations of the disease as well as the treatment and on consideration of emotional aspects (21). Some studies indicate that interventions focusing on expectations of diabetics are effective and result in an improvement of self-care behaviours (22). Interventions aimed at altering disease expectancy have been shown to improve glycaemic control (23).

There is already evidence that a change in expectation for physical diseases such as heart attacks has a positive effect on the symptoms (24). However, for t2dm, there are only a few interventions that aim to improve adherence behaviour via a change in expectation (23). Snoek and colleagues (8) evaluated an intervention focused on identifying and changing negative expectations of type 1 diabetics. The intervention resulted in improved self-treatment behaviour in terms of regular blood glucose control and increased adherence to diet and exercise behaviour (8). There are no comparable studies for type 2 diabetics. Moreover, recent studies found only a small correlation (Cohen's d = 0.04 to 0.13) between disease expectancy and the self-treatment behaviour of patients with chronic diseases (25).

Because of limited evidence on ICBT interventions for patients with diabetes to date, there is a need for further research. Hence, GAIA AG (Hamburg) developed a new intervention (*Covivio*) for adults with t2dm employing CBT techniques to improve adherence and diabetic

self-management. In addition, they developed a psychological online relaxation training (*Relaxio*), which was expected to have a nonspecific effect on diabetes-related variables.

This paper reports the study protocol of a randomised controlled trial comparing the diabetes-specific online intervention *Covivio* to the online relaxation training *Relaxio* and a treatment-as-usual (TAU) control group. The primary objective of the current study is to evaluate the efficacy and specificity of this novel psychological online intervention (*Covivio*). We hypothesise that *Covivio* will be more effective compared to *Relaxio* and TAU in enhancing adherence to diabetes self-care behaviours. The secondary objective is to test the mode of action. We hypothesise that the effect of the *Covivio* and *Relaxio* intervention is related to the expectation of the patients referring to the program. Therefore, the expectation of the treatment is operationalised for the program use and tested for its mediating influence.

3. Methods/Design

Study Design

This randomised controlled trial (RCT) with three parallel groups is registered in ClinicalTrials.gov (NCT03181737). The participants in all three conditions will have unrestricted access to treatment as usual (TAU) during the study. Participants will be screened for inclusion and exclusion criteria via telephone and randomly assigned to either (1) a treatment group that immediately receives 56 days (8 weeks) of access to a novel, internet-administrated diabetes-specific expectation management intervention (*Covivio*), (2) a group that also immediately receives 56 days of access to a psychological online relaxation training (*Relaxio*) or (3) a control group (TAU). They will receive access to the active treatment of choice after completion of all study assessments (see Fig. 1 for study design). Measurement points are scheduled equally for the three groups. They will be collected online at pre-treatment (T0), post-treatment (T1, 2 months after randomisation), and at three- (T2, 5 months after randomisation) and six-month (T3, 8 months after randomisation) follow-ups. After the last follow-up (T3), all participants will gain access to the online program that they had not yet been able to use.

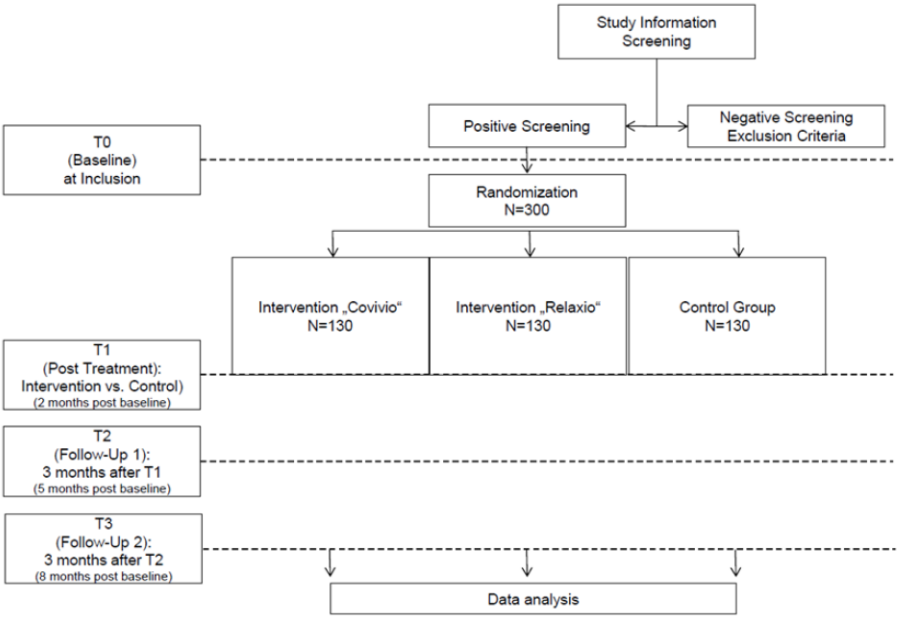

Figure 1 Study design, flow chart

Participants

This study focuses on adults with type 2 diabetes and with currently deficient self-management behaviour.

Inclusion criteria for trial participation are as follows:

(1) Age 18 years or above
(2) Diagnosis of type 2 diabetes mellitus (t2dm)
(3) Currently deficient self-management behaviour as operationalised by a score of less than 7.5 on the Diabetes Self-Management Questionnaire (revised version) (DSMQ-R)
(4) Willingness to participate in regular control (every 3 months) of the HbA1c by physicians during the study period
(5) Ability to speak and read German
(6) Access to the internet and personal possession of an appropriate device on which the internet-based intervention can be used regularly (e.g. smartphone, computer)
(7) Expressed motivation to participate in the trial and use an internet-based intervention to acquire skills and knowledge that might aid in the treatment of diabetes mellitus

Exclusion criteria:

(1) Mental disorder such as bipolar disorder, schizophrenia, other psychotic disorders or borderline personality disorder (based on the SCID-screening interview); or acute and severe physical disease

(2) Acute suicidality (i.e. intention or plan to commit suicide as assessed with the interview)

(3) Newly prescribed diabetes medication or change in diabetes medication dosage in the month prior to study inclusion

Recruitment and Informed Consent

This RCT will include 390 participants with t2dm. Participants will be recruited from various settings including diabetes outpatient treatment centres and internet forums. Methods such as newspaper articles, flyers, posters and media articles will be used to inform potential participants about the study (all material will be in German).

Eligible patients will be screened for inclusion and exclusion criteria via an initial telephone interview. They will be asked to send their latest HbA1c test results from their general practitioner or diabetes doctor or to initiate a first test. Further test results will be collected 2.5 and 8 months later. Participants who fulfil inclusion criteria and sign electronic informed consent will be randomised to one of three treatment groups. Patients in all three groups insigne to maintain regular consultations with their general practitioner or diabetes doctor and to document HbA1c scores as well as patient self-report measures throughout the course of the study (measurement point 1 through 4). Study participation is voluntarily and can be withdrawn at any time without any disadvantages.

Randomisation and blinding

Randomisation follows completion of the baseline assessment. Patients are equally allocated to one of the three treatment groups using an automated procedure. The assignment sequence is generated by staff that is not involved in the intervention process and conducted electronically using the statistical program WINPEPI.

All participants are blinded to the intervention. After baseline assessment, participants in the treatment groups do not know if they will receive access to the diabetic-specific intervention (*Covivio*) or the online relaxation training (*Relaxio*).

Ethics

The study protocol was approved by the local ethics committee of the Philipps University Marburg. The study will be conducted in accordance with the Declaration of Helsinki Good Clinical Practice guidelines including data and patients' privacy protection.

Sample size calculation

The sample size was calculated based on the expected difference in the primary outcome (DSMQ-R) among the intervention groups (*Covivio* and *Relaxio*) and the control group post-treatment. Based on a statistical power of 0.80 (α = 0.05, two-sided test) using the Statistical Power Analyses G-Power (g * power 3.0.8), 130 subjects were required in each group to be able to detect differences with an effect size of 0.35 (16). Compared to other internet studies, we expected a drop-out rate of 20% (9, 16), so we needed to randomise a total study sample of 390.

To achieve clinical significance, we will aim for a minimal reduction of 1 point (SD=1.7) of the sum score of the DSMQ-R to accomplish an optimal HbA1c (26).

Online Interventions

Intervention group *Covivio:*

The *Covivio* program is based on cognitive-behavioural techniques that are intended to support diabetic self-management, specifically medication adherence and lifestyle changes. For example, users are guided on how to set personal goals and how best to implement them, to increase activities in order to reduce anxiety and depression (behavioural activation) as well as to complete exercises for relaxation, stress management and promoting mindfulness.

The *Covivio* program consists of five minimally-guided online sessions (see Table 1 for intervention components). Every session is devised as a tailored interactive "dialogue." The users have the option of several response alternatives (3-5) that determine the further course of the conversation.

In addition, users are required to use the self-monitoring function of the program by answering four questions on regular medication intake, adequate physical exercise (type of sport and activities in everyday life), healthy nutrition and mood. As a result, the "Quality of Lifestyle and Medication Adherence-Index" (QLaMA) is presented along with visualised feedback.

Users are recommended to use the program for eight weeks including one dialogue per week, three times self-monitoring and homework. The average recommended usage time is 60-90 minutes per week.

Taking into account that treatment adherence is a common problem in web-based interventions (18, 19) and that previous studies have outlined the importance of reminders in increasing adherence rates (19), the *Covivio* intervention uses adherence-facilitating features including written dialogue tailored to the users' answers within the program as well as a mobile phone and e-mail support system that offer daily text messages and e-mails.

Intervention group *Relaxio:*

The *Relaxio* program is based on relaxation and stress reduction techniques (see Table 1 for intervention components) that are expected to have a non-specific positive effect on self-management behaviour (27). The structure and intended use of the program is similar the *Covivio* program but without diabetic-specific exercises.

All exercises within *Relaxio* are designed as audio but can also be read as text. They can be repeated as often as required during the intervention period. The individual modules can be presented for 5 to 20 minutes or read at individual speed.

Like *Covivio, Relaxio* also includes an SMS or e-mail service. The users receive a total of 10 SMS or e-mails that include reminders to use the program and tips for relaxation and stress reduction.

Table 1 Intervention components of *Covivio* and *Relaxio*

Intervention *Covivio*	Intervention *Relaxio*
Session 1: Introduction - Programmed introductory conversation with a mascot of the Covivio program	**Imagination exercises** - Guided imaginations of different landscapes and environments
Session 2: Maintaining motivation - Adherence Index: four questions regarding prior drug-taking behaviour - Inner dialogue on medication intake - Reasons for and against drug-intake - Tips for medication managment	**Breathing exercises** - abdominal breathing - diaphragmatic breathing
Session 3: Setting goals - Exercise sheets for setting new personal goals and rewarding oneself - Practical tips for regular drug-intake - Checklist for visiting a doctor	**Physical exercises** - autogenic training - Progressive muscle relaxation
Session 4: Understanding diabetes - Informative audio files addressing bases and symptoms of the disease, diagnosis, long-term effects and therapy	
Session 5: Depression and diabetes - PHQ-9 along with a reference to psychological techniques and medical care - Starting new activities: list of potential new leisure activities - Audio files for practicing mindfulness	

4. Measures

Assessment occurs at four measurement points (see Table 2 for study measures): at baseline, after the intervention (post-intervention) and at 3- and 6-month follow-ups. Questionnaires are applied online at all measurement points.

Demographic and medical information will be obtained at the baseline measurement (T0). The demographic data include age, gender, marital status, nationality, educational achievement, household income and occupation.

The medical information about diabetes: duration, medical treatment (injection, oral), diabetic specific training, attending physician, diabetes complications, accompanying illnesses and medication, Body Mass Index (BMI).

Primary outcome:

Diabetes self-care behaviours will be measured with the German version of the Diabetes Self-Management Questionnaire (revised version) (DSMQ-R) (26). The DSMQ-R determines adherence-related behaviour of patients with diabetes mellitus type 2. It refers to a holistic adherence concept, while the different components are behaviour-related. The DSMQ-R is a 27-item self-report questionnaire that measures self-care activities associated with glycaemic control. The DSMQ assesses five different aspects of diabetes self-management: *dietary control* (DC) (4 items; e.g. "The food I choose to eat makes it easy to achieve optimal blood sugar levels"), *medication adherence* (MA) (2 items; e.g. "I tend to forget or skip my diabetes medication"), *blood glucose monitoring* (GM) (3 items; e.g. "I check my blood sugar levels with care and attention"), *physical activity* (PA) (3 items; e.g. "I am less physically active than would be optimal for my diabetes") and *physician contact* (PC) (3 items; e.g. "I keep all doctors' appointments recommended for my diabetes treatment"). All items are formulated as behavioural descriptions from the patient's point of view. Items are scored on a four-point Likert-type scale ranging from "applies to me very much" (3) to "does not apply to me" (0), referring to the previous eight weeks. A higher item score indicates more desirable self-management behaviour (requiring reverse-scoring of negatively-keyed items). Due to inverted item values, the scale values are calculated as the sum of the items/maximum possible sum of the item's multiplicities with 10. The scale value thus transformed varies between 0 and 10. For this study, the sum score is relevant for the analysis, and the scales are considered. The DSMQ has been shown to display good internal consistency (Cronbach's Alpha = 0.84), and consistencies of the subscales were acceptable (DC: 0.77; GM: 0.77; PA: 0.76; PC: 0.60).

Secondary outcomes:

Medication adherence: Adherence will be measured with the German version of the Medication Adherence Report Scale (MARS-D) (28). This 5-item scale gives an indication of the extent to which non-adherent behaviours occur including how often patients have consciously not taken their medicines or forgotten to take them. It has been used to measure adherence to diabetes treatment before.

Metabolic status: The HbA1c is an objective marker for adherent behaviour in patients with diabetes mellitus type 2. The HbA1c provides information on the blood glucose values of the last 4 to 12 weeks and is collected in standard care every 3 months (29). Body mass index (BMI) is calculated from body weight in kilograms divided by body size in meters squared or BMI = x KG / (y M * y M) (x = body weight in KG, y = size in M).

Physical activity: The Godin-Leisure-Time Questionnaire (GDTQ) is a questionnaire that assesses patterns of exercise behaviour during a person's leisure time (30). Participants should rate their physical activity of the last 7 days (frequency and duration) and the extent/degree (strenuous, moderate, light) of the activity.

Problem Areas in Diabetes: The problem Areas in Diabetes (PAID), a 20-item self-report questionnaire, is used to assess participants' current emotional distress (e.g. fear, anger, frustration) related to living with diabetes (31).

Expectation:

Expectation of Diabetes Self-Management: Expectation will be measured by the adapted version of the diabetes self-management questionnaire (DSMQ-R-E). The original introduction was adapted to: "We are interested in what changes you expect from the use of the online program. The following statements describe behaviours in diabetes self-management. Please indicate which behaviours you expect after using the program." Every single item was converted into a forward-looking statement.

Treatment expectation: Expectations about medication in general as well as specific concerns and necessity beliefs will be assessed with the German version of the Beliefs about Medicines Questionnaire (BMQ). The questionnaire consists of 18 items assessing the cognitive representation of medication on four subscales (32).

Illness expectation: Expectations about time course, consequences, personal and treatment controllability will be measured with the 9-item brief version of the illness perception questionnaire (B-IPQ) (33).

Other outcomes (moderators, control variables):

Anxiety: Anxiety will be measured with the German Generalised Anxiety Disorder Assessment (GAD-7). This 7-item questionnaire is used as a screening tool and severity measure for generalised anxiety disorder (34, 35).

Depression: The Patient Health Questionnaire (PHQ-9) is a 9-item multipurpose instrument for diagnosing, monitoring and measuring the severity of depression (36).

Quality of life: The WHO-Five Well-Being Index (WHO-5) is a 5-item questionnaire used to assess the quality of life of the participants (37).

Treatment evaluation: The subjective usefulness of the program will be measured with individually designed self-report items (38, 39).

Table 2 Study measures

		Baseline pre-intervention	**Post-intervention**	**Follow-up (3 and 6 months)**
Inclusion Criteria	**Interview Measures**			
	Structured psychiatric interview (skid I-screening)	x		
	Demographic and medical data	x		
	Questionnaire Measures			
Primary Outcome	Diabetes adherence behaviour (DSMQ-R)	x	x	x
Secondary Outcome	Adherence (MARS, RAI)	x	x	x
	Metabolic (HbA1c, BMI)	x	x	x
	Physical activity (GLTEQ)	x	x	x
	Diabetes specific strains (PAID)	x	x	x
Expectation Scales	Expectation of Diabetes Self-Management (DSMQ-R-E)	x	x	x
	Illness beliefs (IPQ-B)	x	x	x
	Beliefs about medicines (BMQ)	x	x	x
Process Variables	Anxiety (GAD-7)	x	x	x
	Depression (PHQ-9)	x	x	x
	Treatment evaluation	x	x	
	Quality of life (WHO-5)	x	x	x
Control Variables				

5. Data Analyses

The data of the present study will be analysed on an intention-to-treat (ITT) basis. The DSMQ-R data at post-treatment (T1) will be analysed using an ANCOVA (between-group analyses of covariance) on the individual baseline score of the primary outcome. To measure the between-groups effect size, we will use Cohen's d based on post-treatment group differences (40).

Validated methods such as Jacobson and Truax (41) will be used to calculate clinical significance (42). To show the long-term effect of program use on the primary outcome (after 3 months and 6 months), mixed models should be used.

6. Discussion

The aim of the present study is to evaluate the diabetes-specific self-help online intervention *Covivio* with regard to the self-management behaviour. We expect the DSMQ-R (26) score (primary outcome) of the participants in the intervention group *Covivio* to be significantly higher immediately after the intervention compared to the relaxation (*Relaxio*) and control groups. The planned analyses provide information on whether the outcomes are sustained over time (3- and 6-month follow-ups). Furthermore, we predict that treatment expectation will mediate the correlation relationship.

The *Covivio* program is based on CBT techniques that are intended to support diabetic self-management, especially medication adherence and lifestyle changes (e.g. maintaining motivation, goal setting, knowledge about diabetes and the reduction of depressive symptoms). The *Relaxio* program is based on relaxation and stress reduction techniques that are expected to have a non-specific positive effect on self-management behaviour (27).

Pal and collegues (43) found in their review heterogeneous results regarding the effect of computer-based self-management interventions on individual components of self-management behaviour. Considering that self-management behaviour is a key factor in the treatment of t2dm (44), it should be noted that previous research has focused on single facets. This study tries to capture adherence as a complex set of behaviours. For this reason, the DSMQ-R (26) was used as the primary outcome.

In addition to a direct effect of the intervention group on the self-treatment behaviour, an indirect effect on treatment and disease expectations is also anticipated. Leventhal (45) postulated that patients generate expectations about their disease and treatments, which in turn influence how the patient reacts to them. In addition, they officiate as a mediator regarding the willingness and ability to adapt the adherence behaviour according to the treatment recommendations. *Covivio* tends to use psychological intervention components to positively modify the treatment expectancy of patients with t2dm. This is intended to achieve an improvement in self-treatment behaviour and medication-adherence.

One strength of the study is the ability to modify expectations in order to improve adherence behaviour. There have been preliminary studies with optimisation of expectations in different chronic diseases that showed positive effects (46). However, to date, there are no studies for patients with t2dm.

This study also has some limitations.

Many diabetes patients are elderly, especially those with diabetes type 2, and might have limited access to the internet. Study participation is voluntary. On one hand, particularly impaired patients could be selected out. On the other hand, it is possible that very motivated patients with t2dm will participate in the study. A systematic review found that diabetics with good glycaemic control were more likely to use diabetes-specific online portals than those with poor control. Negative experiences with online interventions also represent a barrier (47). The study does not provide conclusions about single treatment elements.The self-report of the patients with t2dm must be discussed in the term of validity. Thus, the tendency to social desirability, which is defined as adapting one's own behaviour or the description of one's own person to social norms, can lead to a motivated distortion tendency (48). This, in turn, reduces the validity of a measurement. This aspect is of particular importance in capturing adherence behaviour, as it is often overestimated in studies using self-reports (49).

Clinical implications

Covivio is a new self-help online intervention (short duration) to enhance adherence of patients with t2dm. Most interventions are only available in English (50). Previous research focuses mainly on objective measurements (outcomes) such as the HbA1c value for the evaluation of interventions for patients with t2dm. However, this study considers mode of action mechanisms of change in adherence behaviour. In addition, CBT strategies are aimed at optimizing expectations (51), which should positively influence the adherence behaviour. *Covivio* as an online intervention has many benefits. On one hand, due to the high economy, costs for the health system can be reduced (43). On the other hand, a wide distribution of the program can be ensured. Especially in rural areas where medical care is becoming increasingly limited, *Covivio* is a valuable contribution to support patients with t2dm (52). There is no limitation of participants, which allows many patients to work with the program at the same time (43). Most diabetes care services focus on patients who have just received their diagnosis (e.g. diabetes education). It should be considered that many patients are not willing to deal with their self-treatment behaviour at the beginning of their disease (53). However, most will become more motivated later with the occurrence of diabetes-related sequel (54). Until now, individuals with t2dm for long durations who wanted to improve their health status were not adequately supported by the current extent of treatments (11). *Covivio* allows all patients with t2dm to attend regardless of the duration of the disease. If the intervention is effective, the health care system (including health insurance companies) should integrate those web-based programs into the daily routine of diabetes care. In the next step, the interventions should be tested for cost-effectiveness. Effectiveness in routine care should also be demonstrated.

Conclusion

This study will evaluate the web-based intervention *Covivio* for individuals with t2dm and deficient self-management behaviour. This might be a promising pathway to supplement the daily routines of patients with diabetes. The results will provide a recommendation for a possible integration of web-based interventions based on cognitive-behavioural techniques into clinical practice. Furthermore, it is hypothesised that the effect of the *Covivio* and *Relaxio* intervention is related to the expectation of the patients referring to the program. Therefore, this study is the first to operationalise expectation for the intervention and test for its mediating influence.

7. Abbreviations

t2dm: Type 2 diabetes mellitus;

IDF: International Diabetes Federation;

OHA: Oral hypoglycemic agents;

CBT: Cognitive behavioural therapy;

RCTs: Randomised controlled trials;

ICBT: Internet-based cognitive-behavioural interventions;

TAU: Treatment-as-usual;

RCT: Randomised controlled trial;

DSMQ-R: Diabetes Self-Management Questionnaire (revised version);

BMI: Body Mass Index;

DC: Dietary control;

MA: Medication adherence;

GM: Blood glucose monitoring;

PA: Physical activity;

MARS-D: Medication Adherence Report Scale;

GDTQ: Godin-Leisure-Time Questionnaire;

PAID): Problem Areas in Diabetes;

DSMQ-R-E: Diabetes self-management questionnaire (adapted for expectation);

BMQ: Beliefs about Medicines Questionnaire;

B-IPQ: Illness perception questionnaire (brief version);

GAD-7: Generalised Anxiety Disorder Assessment;

PHQ-9: Patient Health Questionnaire;

WHO-5: Well-Being Index;

ITT: Intention-to-treat.

8. Declarations

Ethics approval and consent to participate. The study has received ethical approval from the Local Ethics Committee of the of the Philipps University Marburg, Germany (reference number: 2016-42k-r). The study was registered at ClinicalTrials.gov: NCT03181737 on 09 June 2017 prior to commencement of participant recruitment. All procedures performed in the study involving human participants are in accordance with the ethical standards of the ethics committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent will be obtained from all individual participants included in the study. No animal studies will be carried out by the authors for this research.

Consent for publication. Not applicable.

Availability of data and material. Not applicable.

Competing interests: BM, GJ, are affiliated with Gaia, the e-Health company that funds this trial and that developed, owns, and operates the Internet intervention evaluated in it. BM is employed full-time as research director of GAIA, GJ is employed full-time as research associate. The other authors (AA, JS, WR and YN) declare that they have no competing interests.

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Authors' contributions: AA and JS drafted the manuscript and participate in data acquisition. BM, GJ, WR and YN designed the study and made critical contributions to the conception of the study. All authors have participated in the review and revision of the manuscript and have approved the final manuscript to be published. No professional writers were and will be used.

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B. Curriculum Vitae und Publikationen

(Der Lebenslauf ist nicht Teil dieser Veröffentlichung)

C. Eidesstattliche Erklärung

Hiermit versichere ich, meine Dissertation

„Optimierung der Adhärenz bei Personen mit chronischen Erkrankungen
Prädiktoren, Erfassung, Intervention“

selbst und ohne unerlaubte Hilfe angefertigt zu haben. Ich habe keine anderen als die angegebenen Quellen und Hilfsmittel genutzt.

Die Dissertation wurde in der jetzigen oder einer ähnlichen Form noch bei keiner anderen Hochschule eingereicht und hat noch keinen sonstigen Prüfungszwecken gedient.

Marburg, August 2019

Antje Dorothea Arlt